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Trickey, Adam

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INVESTIGATING THE EPIDEMIOLOGY OF HEPATITIS C VIRUS (HCV) INFECTION IN DIFFERENT SETTINGS AROUND THE WORLD

Adam Trickey

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ABSTRACT

Hepatitis C virus (HCV) is a bloodborne virus affecting the liver. An estimated 71 million people are infected globally and around 400,000 people die annually from HCV-related complications. Direct-acting antivirals (DAAs), highly effective treatments for HCV, were first approved in the US in 2011. Subsequently, in 2016 the WHO developed a Global Health Sector Strategy calling for the global elimination of HCV as a public health threat by 2030. To eliminate HCV requires an understanding of its epidemiology and how it varies across settings, which I investigate in this thesis.

The first part of my thesis involves the use of data from two general population household serosurveys to investigate the risk factors associated with prevalent HCV infections in two high prevalence settings: Pakistan and Punjab state, India. I find various factors associated with HCV infection, including the number of childbirths, or the number of medical injections received; information that is useful to policy makers planning HCV screening strategies in these settings. Additionally, in Pakistan I estimate the contribution of medical, community, and socio-economic risk factors to the HCV epidemic, finding that they all have a large contribution.

The second part of my thesis involves the development of a global model of the HCV epidemics in 88 countries across the world. I use this model to estimate the contribution of injecting drug use (IDU) to country-level HCV epidemics, as well as regionally and globally. I show that, globally, IDU contributes nearly half of all HCV transmission. I use the global model to also estimate the benefit of treatment as prevention for different subgroups of infected individuals. Globally, I find that, of the infected subgroups investigated, the highest number of infections averted are achieved through treating people who inject drugs, while a treat-all strategy will also achieve appreciable prevention benefits.

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My supervisors, Peter Vickerman and Margaret May, have been brilliant throughout this process. I would like to thank them for giving me many incredible opportunities to work on such interesting projects, for dealing with me patiently, and for teaching me so much. Thank you to Public Health England who have funded my PhD through the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Evaluation of Interventions.

Thank you also to my co-authors, collaborators, and those who have helped me with the work in this thesis; particularly Aaron Lim, Hannah Fraser, Jack Stone, Josephine Walker, and Zoe Ward for giving up their time to look at my chapters. I would also like to thank the providers of data used in this thesis.

Although not directly involved with this thesis, I would like to thank my mum and dad, Susie Jacobs and Graham Trickey, for their great support for both the previous three years I was working on this PhD and the previous twenty-six years before that.

AUTHOR'S DECLARATION

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: ……. DATE: …….

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The following four publications form the basis of my four results chapters. Also listed are my contributions to each of these publications.

Trickey A, May MT, Davies C, Qureshi H, Hamid S, Mahmood H, et al. Importance and contribution of community, social, and healthcare risk factors for hepatitis C infection in Pakistan. American Journal of Tropical Medicine and Hygiene. 2017;97(6):1920-8.

"Adam Trickey performed the statistical analyses and contributed to data interpretation and writing the paper."

Trickey A, Fraser H, Lim AG, Walker JG, Peacock A, Colledge S, et al. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis virus infection: web annex 4: modelling analyses. Geneva: World Health Organization. 2018 (WHO/CDS/HIV/18.38).

Trickey A, Fraser H, Lim AG, Walker JG, Peacock A, Colledge S, et al. Modelling the potential benefits of a treat-all hepatitis C treatment strategy at global, regional and country levels: A modelling study. Journal of Viral Hepatitis. 2019; doi: 10.1111/jvh.13187.

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"Conceptualization: Sood A, Suryaprasad A, Kanchi S, Midha V, Alvarez-Bognar F, Garg R, Sharma S, Averhoff F. Methodology: Sood A, Suryaprasad A, Trickey A, Kanchi S, Midha V, Bennett E, Kamili S, Surlikar V, Garg R, Mittal P, Sharma S, May MT, Vickerman P, Averhoff F. Project administration: Sood A, Suryaprasad A, Kanchi S, Midha V, Kamili S, Alvarez-Bognar F, Surlikar V, Averhoff F. Supervision: Sood A, Suryaprasad A, Kanchi S, Midha V, Alvarez-Bognar F, Garg R, Mittal P, Sharma S, May MT, Vickerman P, Averhoff F. Writing – original draft: Sood A, Trickey A, Foster MA, Shadaker S, Averhoff F. Writing – reviewing & editing: Sood A, Suryaprasad A, Trickey A, Kanchi S, Midha V, Foster MA, Bennett E, Kamili S, Alvarez-Bognar F, Shadaker S, Surlikar V, Garg R, Mittal P, Sharma S, May MT, Vickerman P, Averhoff F. Software: Trickey A. Resources: Kanchi S, Alvarez-Bognar F, Surlikar V, Averhoff F. Funding acquisition: Kanchi S, Alvarez-Bognar F, Surlikar V, Averhoff F. Investigation: Kanchi S, Midha V, Mittal P, Averhoff F. Data curation: Foster

MA, Bennett E, Kamili S, Averhoff F. Formal analysis: Trickey A, Foster MA, Bennett E, Shadaker S, May MT. Validation: Averhoff F. Visualization: Averhoff F."

Trickey A, Fraser H, Lim AG, Peacock A, Colledge S, Walker JG, et al. The contribution of injecting drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. The Lancet Gastroenterology and Hepatology. 2019;S2468-1253(19):30085-8

"AT developed the final model, which built on preliminary models developed by HF. AT did the analyses and wrote the first draft of the report, with guidance from PV. PV and NKM had the original idea for the study. PV, MTM, HF, AGL, and JGW supervised the analyses. HF, AP, SC, JL, JG, SL, NKM, LD, MH, and PV contributed to data collection. All authors contributed to data interpretation, writing of the report, and approved the final version."

Another eight papers on hepatitis C virus that have been published from research undertaken throughout my PhD are listed below, as well as my contributions.

Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, et al. Global prevalence of injecting drug use and sociodemographic charactersitsic and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. The Lancet Global Health. 2017;5(12):e1192-e1207

"L. D., S. L., M. H., A. P., J. G., P. V., M. L., and J. L. conceived of and designed the scope and methods of the study. All authors made substantial contributions to the acquisition of data. S. C., J. L., A. P., and L. D. conducted the analysis and generated the estimates. J. L., S. C., S. L., J. G., A. P., M. H., and L. D. contributed to the interpretation of data for the manuscript. J. L., A. P., S. C., and S. L. drafted the first iteration of the manuscript. All authors contributed to revising the manuscript critically for important intellectual content. All authors approved the final version of the study to be published and are accountable for all aspects of the work. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication."

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"P.V., F.A. and N.G. initiated the study with the Pakistan HCV Technical Advisory Group (H.Q., H.M., S.H. and Q.S.). P.V. provided overall leadership for the study design, analysis and interpretation of the findings. F.A., N.G. and the Pakistan TAG guided the analysis plan developed by P.V. and A.G.L. A.G.L. developed the final model, with preliminary models developed by H.F. and C.M. A.G.L. performed all model analyses. A.T., M.M. and C.F.D. undertook analyses of the National Survey dataset and blood donor data for parameterizing the model. H.Q., H.M. and S.H. provided data for the model. A.G.L. wrote the first draft of the manuscript with P.V. All authors have contributed to the overall collaboration through guiding the analysis plan, interpreting the results and writing subsequent versions of the manuscript."

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"AT performed the analyses and wrote the first draft of the paper. PV and MH had the original concept for the study. MTM, PV, and MH supervised the analyses. VH, MD, and EH collected and provided the data. VH and PV oversaw question design. AT, MTM, VH, ZW, MD, EH, MH, and PV contributed to data interpretation, writing the report, and approved the final version."

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"Adam Trickey contributed to the acquisition of data, to revising the manuscript, and approved the final version of the manuscript."

Stone J, Fraser H, Lim AG, Walker JG, Ward Z, MacGregor L, et al. Incarceration history and risk of HIV and hepatitis C virus acquisition among people who inject drugs: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2018;18(12):1397-1409

"JS and PV were responsible for conception and design of the study, aided by MH. JS did the literature searching and data analyses, with the guidance of PV and MH. JS, HF, AGL, JGW, ZW, LMac, AT, and SA contributed to the screening. JS and HF were responsible for data extraction. JS and PV contacted cohorts to request unpublished data. SAS, DA, LMah, JI, RSG, Y-FY, TA, SHM, MJM, MEH, RS-D, MAlar, TT, VM, MAlad, ER, PS, YS, AMY, JRH,

VDH, MD, EH, SJH, NEP, AM, PMD, CA, JB, and GZ contributed unpublished data for the study. SAS, DA, LMah, JI, RSG, Y-FY, SHM, MJM, MEH, RS-D, MAlad, MAlar, ER, PS, YS, VDH, MD, EH, LP, PMD, CA, JB, GZ, JGW, and JS did additional analyses on the unpublished data. JS and PV wrote the first draft of the manuscript and all authors contributed to interpretation of data and critical revision of the Article."

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"GGK, KWYK and RVdB conceived and designed the experiments. GGK, SK and KA performed the experiments. GGK, KWYK, RVdB and AT analysed the data. KWYK, RVdB and AT contributed reagents, materials and analysis tools. GGK, RVdB and KWYK wrote the paper. All the authors approved the manuscript."

Leung J, Peacock A, Colledge S, Grebely J, Cunningham EB, Hickman M, et al. A global meta-analysis on HIV, hepatitis C and hepatitis B among people who inject drugs-do gender differences vary by country-level indicators? The Journal of Infectious Diseases. 2019;jiz058

"L. D., S. L., M. H., A. P., J. G., P. V., M. L., and J. L. conceived of and designed the scope and methods of the study. All authors made substantial contributions to the acquisition of data. S. C., J. L., A. P., and L. D. conducted the analysis and generated the estimates. J. L., S. C., S. L., J. G., A. P., M. H., and L. D. contributed to the interpretation of data for the manuscript. J. L., A. P., S. C., and S. L. drafted the first iteration of the manuscript. All authors contributed to revising the manuscript critically for important intellectual content. All authors approved the final version of the study to be published and are accountable for all aspects of the work. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication."

Lim AG, Trickey A, Vickerman P. Screening strategies for hepatitis C virus. Hepatology Communications. 2019;3(3):321-324

"Adam Trickey and Aaron Lim jointly conceived the contents of the article. Adam Trickey contributed to the revising of the manuscript and approved the final version."

The document below contains the agreed author declaration statements for Adam Trickey's participation in articles he contributed to, which were published during the course of his PhD. The articles listed are those published without author contribution statements. For these articles, declaration statements for Adam Trickey's contribution have been drawn up with the agreement of the co-authors. These declaration statements are signed by the first and final authors of each publication.

Trickey A, May MT, Davies C, Qureshi H, Hamid S, Mahmood F, et al. **Importance and contribution of community, social, and healthcare risk factors for hepatitis C infection in Pakistan.** American Journal of Tropical Medicine and Hygiene. 2017;97(6):1920-8.

"Adam Trickey performed the statistical analyses and contributed to data interpretation and writing the paper."

First author: Adam Trickey

Final author: Peter Vickerman – signed: [redacted]

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"Adam Trickey developed the final model, performed the analyses, and wrote the first draft of the report."

First author: Adam Trickey

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Lim AG, Trickey A, Vickerman P. **Screening strategies for hepatitis C virus.** Hepatology Communications. 2019;3(3):321-324.

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Grebely J, Tarney S, Peacock A, Colledge S, Leung J, Hickman M, et al. **Global, regional, and country-level estimates of hepatitis C infection among people who have recently injected drugs.** Addiction. 2018;114(1):150-166.

"Adam Trickey contributed to the acquisition of data, to revising the manuscript, and approved the final version of the manuscript."

First author: Jason Grebely – signed: [redacted]

Final author: Louisa Degenhardt – signed:

CHAPTER 1. INTRODUCTION

Hepatitis C virus (HCV) is a bloodborne virus that was first identified in 1989(63). HCV affects the liver, with some infected individuals developing cirrhosis of the liver and liver cancer(331). In 2015 there were an estimated 71 million people infected with HCV, globally(40), with 1.75 million incident infections occurring annually(406). Around 400,000 people are thought to die of HCV-related complications every year(407). In 2016 the World Health Organization (WHO) developed targets to eliminate HCV as a public health concern by 2030(403). These targets include reducing the number of incident infections by 80% and HCV-related mortality by 65% from the 2015 levels(403). The WHO released these targets following the development of direct acting antiviral (DAA) treatment for HCV(51). DAAs result in sustained virologic response rates (an effective cure) of 95%, far above the levels of previously available interferon-based treatments(51). Since the development of DAAs and the WHO releasing their elimination targets, countries have scaled up their commitments to tackling HCV(409). However, in order to eliminate HCV, an understanding of its epidemiology is required. Such an understanding will allow policy-makers to know who to target for HCV testing and treatment, which could improve the yield of infected people from testing and the prevention benefit of treatment, which could in turn reduce the costs associated with HCV elimination when there are many competing healthcare priorities requiring investment.

The WHO's 2018 Access to HCV Treatment Report(409) tracks the progress that has been made as more countries use DAAs to treat HCV. An example of a country where there has been huge progress is Egypt, which has one of the highest prevalences in the world, estimated at 10.0% in 2015(181). Due to its high burden, the epidemiology of HCV in Egypt has been well studied compared to most other countries. Knowledge of the epidemiology of HCV in Egypt and the considerable burden it will take on the health system has in part led to substantial political support to meet the WHO's elimination targets; starting in October 2018, in four months around 30 million people were tested for HCV in Egypt(11).

However, for the vast majority of countries progress has been much less than in Egypt, partially due to a lack of understanding of the epidemiology and healthcare burden of HCV in those countries(409). The importance of different transmission routes for HCV has evolved over time(95, 267). Unsafe blood transfusions were previously the most common route of transmission globally, although this has reduced considerably due to the

introduction of blood screening, which happened at different times in different countries, and to varying standards(291). Following this, the use of unsterile medical injections and other medical procedures is thought to have made up a larger proportion of the new infections, as well as the sharing of equipment related to injecting drug use (IDU)(95, 283). Other modes of infection have also been reported, such as sexual transmission(357), child birth(35), or using a barber that does not sterilise their blades(259). For many countries, there is uncertainty around the main risk factors that are associated with HCV infection and the importance of different routes of transmission to each country's epidemic have not been quantified. In high-income countries it is often assumed that most of the transmission is due to IDU, however, this is less certain in low- and middle-income countries. Additionally, the full epidemiological benefits of treatment have been little studied in terms of how treating infected individuals will not only cure that person of HCV but will prevent further onwards transmission. This prevention benefit could be affected by the different characteristics of the epidemic in each country, so understanding the epidemiology of HCV in that setting is important for understanding the impact of treatment. This thesis focuses on the epidemiology of HCV in different settings around the world, looking at where different risk factors are important and investigating the possible impact of treatment as prevention.

In chapters 4 and 5, I look at the factors associated with HCV prevalence in settings where the epidemic is considered high prevalence and generalised, meaning that it is not focused among a particular subgroup, such as people who inject drugs (PWID). Elucidating the factors associated with HCV prevalence is of use for minimising the use of resources and increasing the yield when designing HCV testing programs to identify those who are unaware of their infection status. The WHO estimated in 2017 that the percentage of infected individuals that are diagnosed is around 20%(406). In Pakistan, where the prevalence has been estimated to be as high as 4.9% nationally and even higher in the Eastern provinces(295), the initial stages of a large treatment program are underway(255, 295). In chapter 4 I use the data from Pakistan's 2007 national HCV serosurvey, to investigate the factors associated with HCV as well as calculating population attributable fractions to investigate the contribution of medical, community, and social factors to the epidemic in that setting. In chapter 5, I move across Pakistan's Eastern border to Punjab, India, where I present the results of a recent HCV serosurvey from 2013-2014. This is another high prevalence setting, with a previously estimated prevalence of 5.2%(344). Like Pakistan, Punjab has a generalised (as opposed to a concentrated) epidemic, but has seen growing

reports of IDU(326). I once again use a serosurvey to investigate which factors are associated with being HCV positive and compare between the two settings.

In chapters 6, 7, and 8, I use mathematical modelling to investigate the epidemiology of HCV in 88 countries spread across the globe. Chapter 6 describes the model and methods used for the analyses in chapters 7 and 8. In chapter 7, I move from looking at two generalised epidemics in Pakistan and Punjab, India, to investigating the contribution of IDU to HCV epidemics across all countries where sufficient data are available. Whilst the previous chapters had looked at the associations with prevalent HCV infections, the analysis in chapter 7 focuses on HCV incidence, estimating the percentage of transmission that would be avoided if the HCV epidemic among PWID could be fully controlled, i.e. I remove the additional transmission due to the sharing of unsafe injecting equipment. The 88 countries included in this modelling exercise are diverse and cover most of the world's population, allowing me to estimate the contribution of IDU to HCV transmission for different regions, as well as to produce a global estimate. Importantly, we are also able to get insights into how country-level factors affect the contribution that IDU makes to these epidemics. Although such estimates highlight the importance of focusing resources to prevent transmission among key populations such as PWID, they also give information on how their importance varies globally, which is useful for prioritising resources for achieving the WHO's HCV elimination targets.

After the previous results chapters have investigated the epidemiology of how people became or become infected with HCV, chapter 8 uses the model from chapter 7 to get insights on the benefits that will be achieved through intervening on these epidemics in the form of treatment as prevention(156). I quantify this benefit for various subgroups, including PWID. These analyses were commissioned by the WHO, with there being a focus on determining the prevention benefits of a treat-all strategy, which subsequently fed in to the WHO's 2018 recommendation to expand HCV treatment to all, for which chapter 8's analyses are published as an appendix(410). Quantifying the prevention benefit of treatment allows policy makers to plan how intervening on their HCV epidemic will affect the future transmission and burden of HCV, which is crucial data in these early years of DAA availability and the era of HCV elimination.

I begin this thesis by providing a background to HCV and its epidemiology in chapter 2, as well as presenting a background to the mathematical modelling of infectious diseases, particularly HCV, in chapter 3.

CHAPTER 2. A BACKGROUND TO THE GLOBAL HEPATITIS C VIRUS EPIDEMIC

2.1. Introduction

The topic of this thesis is the epidemiology of hepatitis C virus (HCV) epidemics around the world. This background chapter describes the global HCV epidemic in six sections. The first section discusses the natural history of HCV, the second focuses on the transmission routes of HCV, whilst in the third section I discuss the risk factors of HCV infection. Within the fourth and fifth sections of the chapter, I discuss prevention and treatment strategies for HCV. In the sixth section I review data on HCV prevalences and genotypes across and within different regions.

2.2. HCV natural history

2.2.1. Description of HCV and infection

HCV was first identified in 1989(63). It is an enveloped, single-stranded RNA virus from the Flaviviridae family of the hepacivirus genus(216). HCV is a bloodborne virus that infects the body's liver cells causing hepatitis C disease within the liver(331). Most HCV infections occur via unscreened blood transfusions, unsterilised medical procedures, and the sharing of needles and syringes for injecting drug use (IDU)(16). The initial stage of HCV infection is the acute stage, which can then either progress to lifelong chronic disease or, in an estimated 26% of infections, can clear spontaneously(252, 390). Without treatment, chronic hepatitis C infection can lead to cirrhosis of the liver and hepatocellular carcinoma, which in turn can lead to the death of the infected individual(369). The virus is genetically variable, with there being seven major HCV genotypes that can be divided further into sixty-seven subtypes(340). All infected individuals develop an HCV antibody response. However, diagnosis of active HCV infection is done through testing for HCV RNA, for which a positive result indicates a current, acute or chronic HCV infection(195).

2.2.2. Acute and chronic infection

Upon becoming infected with HCV, individuals are in the acute phase of hepatitis C disease. Around 15% of individuals exhibit symptoms in this acute phase(227). These symptoms tend to be mild but can include jaundice in some instances(227) and in very rare, severe cases can also lead to death(159). Spontaneous clearance of acute infection can depend on various factors including gender, age, genotype, and HIV co-infection status(7). Following spontaneous clearance, there are no additional HCV-related side-effects in that individual(390), but it is uncertain whether the individual will be protected from HCV reinfection or if they are genetically more likely to clear the infection(126, 167, 188, 316). Individuals that spontaneously clear an infection are more likely to do so again(126). The majority who spontaneously clear the infection do so within the first six months and those who have not cleared it after twelve months are unlikely to do so(7). However, determining the timescale for how long HCV RNA must persist within the body following the initial infection, to define chronic infection, is difficult. This is due to the generally asymptomatic nature of the acute phase of infection, meaning the date of transmission is unknown in many cases(390).

2.2.3. Disease complications and survival

Early chronic infections tend to be asymptomatic(232). The disease progresses slowly, and cases may go undiagnosed until individuals present with symptoms of end-stage liver disease(320). Years of inflammation due to untreated HCV infection can cause cirrhosis of the liver, which is estimated to affect around 16% of patients with chronic infection after 20 years(366). The rates of progression to cirrhosis are affected by alcohol consumption and HIV co-infection, among other factors(320). For those with cirrhosis, there is a 3-6% annual risk of developing hepatic decompensation(390). Hepatic decompensation is defined as the rapid development of one of a range of clinical compensations including ascites and hepatic encephalopathy(314). Individuals with compensated, as opposed to decompensated, cirrhosis are also at risk of developing hepatocellular carcinoma, at a rate of roughly 1-5% annually(390). For untreated, chronically infected individuals with cirrhosis, the liver-related mortality rate is around 7% per year, with the main HCV infection-related prognostic factors for mortality being the level of cirrhosis and whether they have

developed hepatocellular carcinoma(140). The 5-year survival rate for decompensated cirrhosis is 50%(100)

2.2.4. Genotypes

There are seven distinct HCV genotype variants that are further classified into sixty-seven subtypes(340). There is considerable regional variation in the distribution of the HCV genotypes(285), which will be discussed further in section 2.7.3. Until the recent development of the pan-genotypic direct-acting antivirals (DAAs)(51, 420), the effectiveness of treatments for HCV was hampered by the variation in genotypes and subtypes(51, 420), with available treatments having different levels of effectiveness for different genotypes(51). This resulted in clinicians having to consider the genotype of their patient when prescribing treatment, with genotype tests being time consuming and expensive(108, 289).

2.2.5. Disease diagnosis

Diagnosis of HCV rarely occurs during the acute phase of infection because it is mostly asymptomatic and usually brief so unlikely to be detected by screening. Therefore diagnosis is far more common at later phases of the infection(195). HCV antibody tests, such as the enzyme-linked immunosorbent assay (ELISA), can determine whether an individual has ever had acute infection(131). However, a positive HCV antibody test result does not indicate whether that individual spontaneously cleared their infection or is currently infected(131). HCV RNA tests, such as the nucleic acid test (NAT), or an HCV core antigen test, for example the chemiluminescence immunoassay (CLIA), are required to ascertain whether an active infection is present(131). A negative result for an HCV RNA or HCV core antigen test indicates there is no current HCV infection in that individual(131). HCV core antigen tests tend to be cheaper than HCV RNA tests but have been limited by their lower sensitivity, although this is not necessarily the case for recently developed core antigen tests, such as the ELISA(131). Recently, point of care tests with high diagnostic accuracy for detecting active infection have been developed, although currently they are not widely used due to high costs(214). The World Health Organization regularly updates its guidelines on hepatitis B and C testing, with the 2017 version declaring NAT testing for HCV RNA to be the preferred strategy for diagnosis of chronic infection(404).

2.3. HCV transmission routes

2.3.1. Historical and geographical differences in transmission routes of HCV

An individual becomes infected with HCV through being exposed to blood contaminated with the virus(16). How people tend to come into contact with infected blood varies by region and country with these modes of exposure having changed over time(16, 283, 291). In high-income countries, the primary mode of transmission was through contaminated blood transfusions until blood screening was introduced in the early 1990s(291). Since then IDU has become the primary transmission risk factor in these countries(95). Though most low- and middle-income countries have now introduced blood screening, there is still transmission in healthcare settings in many countries(342). For these countries, blood screening methods are often sub-optimal and there is additional healthcare-related transmission through unsterilised equipment(342). In low- and middle-income countries with poor healthcare practices, IDU generally contributes less to transmission than in high-income countries(342). Besides iatrogenic and IDU-related transmission, HCV infections can also occur through community(16, 371) and household activities(74, 139), mother-to-child transmission(37, 417), and sexual transmission(44, 357).

2.3.2. Iatrogenic transmission

Iatrogenic transmission of HCV is thought to be mostly through contaminated blood transfusions and the re-use of unsterile medical equipment. High-income countries introduced robust methods of blood screening in the early 1990s(291). Following this, the transmission risk due to HCV contaminated blood declined sharply from around 1 in 50 units to around 1 in 200,000 today(291). Most, but not all, low- and middle-income countries have now introduced blood screening, with the WHO reporting for 2013 that 81% of donations are screened in lower-middle-income countries and 66% in low-income countries(405). However, the screening techniques used in less wealthy countries are often less able to detect infections than in high-income countries; a review of screening tests used in selected African countries found 80% sensitivity, possibly due to the prohibitive costs of the best screening tests(208). Haemophiliacs are particularly affected by poor screening of blood donations as their condition means they require a high quantity of transfusions and these are concentrated from many donations to produce factor VIII, an essential blood-

clotting protein(279). The use of unsterile medical equipment, particularly therapeutic injections, is still a major transmission route for many countries(16, 283). This is despite an almost ten-fold decline in the global re-use of syringes between 2000 and 2010(282). This re-use of medical syringes can be due to a lack of sterile equipment among health providers, some of whom are not professionally trained and are unaware of the transmission risks(16). Evidence suggests historic vaccination campaigns with poor sterilisation practices, such as for schistosomiasis in Egypt in the 1950s, have led to HCV epidemics in certain settings(94). Healthcare related HCV transmission is very rare in high-income countries, although occasional reports are seen(75). Globally, iatrogenic transmission of HCV is either declining as countries introduce improved blood screening measures combined with less re-use of unsterile injecting equipment, or has already reached a very low level, depending on the setting(267, 283).

2.3.3. Transmission via injecting drug use

There is a high risk of HCV transmission for people who inject drugs (PWID) that use unsterile injecting equipment passed on from others, such as needles, syringes, filters, and water(16). A 2017 review estimated that 0.2-0.3% of adults inject drugs globally; about 14.9 million people(77). Around 39% of PWID are chronically infected with HCV(127) with estimated chronic prevalence among PWID varying between 29% and 49% across regions, except for Sub-Saharan Africa where it is 16%(127). IDU in Sub-Saharan Africa is thought to have started more recently than in other regions, possibly explaining this discrepancy(119). Other factors are also important for explaining regional variations in HCV prevalences among PWID, including drug availability, differences in the coverage of prevention measures, or different risk behaviours. Estimates of chronic HCV prevalence among PWID are as high as 71.5% in Mexico, where almost all PWID, 97.4%, have been exposed to HCV(77, 127). Similar figures are seen in other countries, such as Taiwan, Portugal, Estonia, and Mauritius, where around 90% of PWID have been exposed to HCV and estimates of chronic prevalence are only slightly lower than in Mexico(77). Of all current prevalent HCV infections, around 8.5% are among PWID(127). However, through a study discussed at length in chapter 7 and published in the Lancet Gastroenterology and Hepatology, I estimate that around 43% of incident infections globally are due to the risks associated with IDU and more than 90% in many high-income countries(68, 373).

2.3.4. Mother-to-child transmission

Mother-to-child transmission is a major source of HCV infection among infants, particularly in high prevalence settings such as Egypt(36). Mother-to-child transmission is also referred to as perinatal or vertical transmission. Data suggests that this transmission happens in utero and that there is no association between breastfeeding and transmission(69). The risk that a mother infected with HCV will pass the virus onto her child is around 5.8%(35). On average, mothers that transmit the virus to their child have higher viral loads than those who do not(35). For mothers that are HIV co-infected, the risk of HCV transmission is 10.8%(35). This higher rate among HIV co-infected mothers is possibly explained by HIV causing an elevated HCV viral load(20).

2.3.5. Sexual transmission

Rates of sexual transmission of HCV are thought to be low but as sex is common it could possibly impact HCV epidemics globally. A study examining incidence of sexual transmission in HCV-discordant heterosexual couples found the transmission rate to be low, 3.7 per 10,000-person-years(383). However, HCV incidence among men who have sex with men (MSM) is higher than among heterosexual couples, estimated at around 14.8 per 10,000-person-years(414). This could be due to an increased risk of blood contact or is possibly due to a higher prevalence of risky sexual practices among MSM such as chemsex that can combine IDU and sex, making the actual route of transmission hard to determine(83). The HCV incidence rate is even higher among MSM that are HIV-positive, with one study finding a rate of around 60.8 per 10,000-person-years(414), and another finding 134.0 per 10,000-person-years in 2012(135). Intentionally coupling with partners that are also HIV-positive is thought to have led to an increase in unprotected anal sex among MSM, possibly explaining the elevated HCV incidence rate in this group in recent years(44). However, for both heterosexual couples and MSM, it is difficult to separate out transmission between partners through sex or via shared behaviours and household activities(166). Therefore, the actual rate of sexual transmission could be lower than current estimates(166).

2.3.6. Transmission via community and household activities

HCV transmission through community and household activities can happen in many forms. Community transmission routes include a barber using unsterilised shaving equipment(259), someone receiving a body-piercing(163, 367, 413) or a tattoo(53, 172, 367), or religious or cultural rituals, such as Matam(274, 371), circumcision(281), or female genital cutting(187). Household activities leading to HCV transmission include the sharing of toothbrushes(219) or shaving equipment(419). Evidence of HCV transmission exists for all these behaviours but is weaker than for other transmission routes(16, 163, 412). The evidence to date is mostly based on bio-behavioural surveys where these household and community activities are associated with HCV prevalence(163), although not in all instances(381). These bio-behavioural surveys may over-predict the importance of community and household transmission routes to HCV epidemics in settings where another transmission route is very common within the population, such as the use of medical injections in India, in a study discussed in further detail in chapter 5(346). Therefore, the extent to which these activities contribute to HCV epidemics is unclear, but in countries with generalised epidemics their impact on maintaining the epidemic could be substantial because most are common behaviours, particularly piercing, barbering, and tattooing(294, 412). The prevalence of these behaviours varies by gender(43) and age(199), and across cultures(274). The risk of HCV transmission for most of these community behaviours can vary by country, depending on the sterilisation procedures of the practitioners(172).

2.4. HCV risk factors

2.4.1. Introduction

Many risk factors that are not themselves HCV transmission routes are associated with elevated prevalences of HCV within populations. These risk factors include homelessness, low socio-economic status, living in rural areas, being a prisoner, and being a migrant from a high-prevalence country. Many, if not all, of these factors are high-risk due to their association with particular transmission routes, for example, among prisoners and the homeless there is a high prevalence of IDU(198, 311). Nonetheless, consideration of these risk factors is important for the implementation of screening programs, where targeting of

population subgroups is required to reduce the amount of people screened and to increase the yield of testing.

2.4.2. HCV among prisoners

Results from a meta-analysis estimated the prevalence of anti-HCV among prisoners to be 15%(81). Anti-HCV prevalence among prisoners varied by region, with all regions studied having an estimated prevalence above 10% except for Latin America (4.7%) and east and southern Africa (1.8%)(81). The regions with the highest anti-HCV prevalences among prisoners are Asia Pacific (20.6%), and Eastern Europe and Central Asia (20.2%)(81). PWID are overrepresented in prisons; a systematic review found that around 58% of PWID had been incarcerated(77). Additionally, evidence shows that recent incarceration is associated with a 62% increase in risk of HCV acquisition among PWID(350), possibly due to a period of heightened transmission risk following release, or increased risk during imprisonment(350). Despite being outlawed, IDU occurs within prisons where in many cases there is a lack of sterile injecting equipment, which can lead to an increase in use of unsterile equipment(418). Aside from IDU, prisons can be places of increased HCV transmission due to tattooing with re-used needles or ink, behaviours that are common(153). Due to this combination of factors, modelling in Scotland, the USA and Eastern Europe suggests that incarceration can be important drivers of HCV epidemics(17, 147, 349).

2.4.3. HCV among the homeless

Homelessness is associated with IDU and, as discussed, PWID have elevated prevalences of HCV. PWID report high levels of housing instability(368), which is exacerbated by PWID often being incarcerated for drug offences(368). Research also suggests that homelessness is associated with the initiation of IDU as drugs are used by homeless people to cope with the hardships of sleeping rough, as well as mental illness(368). A global meta-analysis of studies on homeless people found a pooled HCV prevalence estimate of 20.3%(33).

2.4.4. Socio-economic status and HCV

Various studies, including in the USA, Denmark, Vietnam, and Pakistan, have found a positive association between poverty and HCV prevalence(78, 271, 379, 388). After adjustment for IDU and other route-of-infection related risk factors this association between low socio-economic status and HCV remained for some studies(249, 284). One suggested reason for this association is the under-classification of PWID in these studies(271). In low- and middle-income countries, where medical transmission of HCV is more common, an explanation for this association could be due to increased use of unsterilised medical interventions in areas with more poverty(379).

2.4.5. HCV and the urban/rural divide

Prevalences of HCV in urban and rural communities have been compared across many countries, including India, Nigeria, and China(105, 293, 346). Most studies in low- or middle-income countries have found higher prevalences of HCV in rural communities than in urban communities(105, 346, 422). For these countries where medical HCV transmission is still an issue, this is possibly due to people living in urban areas having better access to healthcare facilities such as hospitals, or due to particular traditions being more prevalent in rural areas, such as scarification(114). In contrast, a US study found that the states with the highest HCV prevalences tended to be those with highly urban populations(312), probably reflecting higher proportions of PWID in cities(312), although this could have changed in recent years with an increase of IDU in some rural areas(110). For higher-income countries in general where access to high-quality healthcare is good in both urban and rural areas, rural-urban differences in HCV prevalences most likely are driven by the distribution of PWID.

2.4.6. HCV among migrants

The migration of HCV-infected persons can have a large effect on the HCV prevalence in the destination country(385). A modelling study in the Netherlands concluded that the majority of infected persons in the country were migrants(385). Whilst migrants from high prevalence countries might be expected to have the same prevalence as their country of origin, two

systematic reviews found instances of slightly lower prevalences(99, 128). Discrepancies between HCV prevalences of migrants and the countries they migrated from could possibly be due to a healthy migrant effect where only the healthiest are able to migrate(128). The prevalence of HCV among migrants varies across countries, depending largely on HCV prevalences of the countries of origin(40, 99). One study estimated that migration accounted for 34% of new infections in the EU in 2015, although this was a year with especially high levels of migration(302).

2.5. HCV treatment

2.5.1. Introduction

The aim of treatment for HCV is to rid the infected person of the virus, so reducing the chance of cirrhosis and other complications(337). The measure for determining whether HCV treatment has been successful is a patient's sustained virologic response (SVR) 12 weeks after completing treatment, whereby they are assumed to be cured if they have an undetectable HCV RNA viral load(51). The history of HCV treatment can be split into two eras, with the first starting soon after the discovery of hepatitis C in 1989(51). In this first era, the main treatment for HCV was using interferon, or variants of, which was approved by the US Food and Drug Administration (FDA) in 1991(51, 107). In 2011, the US FDA approved the first DAAs, heralding the second era of vastly superior HCV treatments(51, 102). However, most countries did not have access to DAAs in 2013 and some countries still do not have access to them in 2019(409).

2.5.2. Interferon-based treatment

The first interferon (IFN) based treatment regimens for HCV were for either 24 or 48 weeks and were administered by injection(51, 230, 248). SVR was seen in 6% of patients for the 24-week regimen, and 15-20% for the 48-week regimen(230, 248). Interferon regimens were combined with ribavirin (RBV) in the 1990s to raise the SVR percentages to around 40-50%(230). The US FDA approved pegylated IFN (PEG-IFN) for HCV treatment in 2002(247), increasing IFN's half-life and raising the SVR percentages(51, 107). However, these SVR

percentages varied by HCV genotype(231). For people with genotype 1, SVR rates of 42-46% were achieved for 48-weeks of PEG-IFN/RBV(231). However, much higher SVR rates were seen for people with genotypes 2 or 3, around 76-82% for a 24-week regimen(231). For all of these IFN-based regimens, high percentages of patients reported severe adverse effects such as the onset of depression and anaemia due to an abnormal breakdown of red blood cells(230). These adverse effects often resulted in dosage reductions and, for around 10-20% of people, stopping treatment(111, 230). The combination of treatment taken by injection for long periods of time, severe side effects, and low success rates stopped people receiving PEG-IFN/RBV and gave many a poor opinion of HCV treatment.

2.5.3. Direct acting antivirals

The 2011 US FDA's approval of boceprevir and telaprevir ushered in an era of more effective HCV treatments(51, 391). These first DAAs were taken in combination with PEG-IFN/RBV and led to improved SVR percentages of around 75% for genotype 1 patients that previously had much lower SVR percentages with just PEG-IFN/RBV(51, 102). In 2013 the US FDA approved two new DAAs, sofosbuvir and simprevir, both of which were taken in combination with RBV but without PEG-IFN(51). The development of IFN-free regimens meant the availability of HCV treatment with high SVR rates and few adverse effects(102). Additionally, these DAAs are taken in the form of a pill rather than administered by injection and involve much shorter courses of treatment of around 12 weeks(24). Unlike the first generation of DAAs, the second generation could be used to treat patients that did not have genotype 1(24, 51). For these initial IFN-free DAA regimens there was still some variation in SVR by genotype, with around 85% observed for genotype 1 and over 90% observed for other genotypes(51). Since the approval of the first IFN-free DAA regimens, many others have been developed, with even higher SVR percentages(102). Importantly, the very latest generation of DAAs have close to 100% SVR percentages for all genotypes(161). Today's DAAs are easy to administer, highly tolerable, and very effective across all populations studied(138).

2.5.4. Access to direct acting antivirals

Although highly effective DAAs have been developed, they are not available in all countries due to issues around costs(409). However, in some countries, almost exclusively low- and lower-middle-income countries, where patents do not cover DAAs, generic drug manufacturers have set up production(409). The WHO report large price reductions have occurred for DAAs since 2015, with the lowest prices reported by originator companies dropping from 300 US dollars (USD) per 28-day supply to 250 USD in 2017, and comparative prices of generics dropping from 300 USD to less than 50 USD(409). Increased competition has driven these price drops, particularly from generic manufacturers, however, not all countries where cheaper generic versions of DAAs are available have taken the opportunity to purchase them(409). Where generics are unavailable in high-income and most upper-middle-income countries, DAAs are very expensive, for example, a 28-day supply of sofusbuvir and velpatasvir cost between 10,500 and 17,000 USD in the UK in 2016(409). Other high-income or upper-middle-income countries have found such prices to be too restrictive and have instead continued to use the much cheaper IFN-based regimens, for example Kenya(157). However, the situation regarding treatment availability and pricing is changing rapidly as countries negotiate directly with the manufacturers and prices continue to fall(409).

2.6. HCV transmission prevention

2.6.1. Introduction

Various interventions have been developed to prevent HCV transmission. Besides reducing the number of people exposed to a deadly virus, preventing the transmission of HCV reduces the number of treatments required. Transmission prevention interventions vary from those that affect most of the population, such as blood screening(243), to those targeted at specific subgroups of individuals, such as needle and syringe provision for PWID(212). Prevention also occurs due to the reduction of onwards infections from treatment itself(421).

2.6.2. Iatrogenic transmission prevention

The most effective transmission prevention intervention to date has been the advent of blood screening(291, 330). As discussed in section 2.3.2, HCV transmission in high-income countries decreased from roughly 1 in 50 units to around 1 in 200,000 following the introduction of blood screening(291). Section 2.3.2 also mentioned that between 2000 and 2010 there has been around a ten-fold reduction in the re-use of medical syringes(282). This has coincided with an estimated 83% decrease in the number of HCV infections due to medical syringe re-use from between 0.95-1.87 million in 2000 to between 0.16-0.32 million in 2010(283). This large decrease in the re-use of medical syringes is due to various awareness campaigns led by health ministries, health providers, and the WHO Safe Injection Global Network (SIGN)(282). Some initiatives have been developed to increase the awareness of iatrogenic transmission of HCV among healthcare workers but the effectiveness of these interventions on HCV transmission has not been evaluated(184, 228, 272).

2.6.3. Counselling

There is limited evidence to suggest that counselling people at heightened risk of HCV, or that are HCV-infected, reduces transmission. A study aiming to reduce HCV risk behaviours among PWID compared the effect of a questionnaire against a questionnaire plus a brief behavioural intervention(2). Both methods produced a reduction in HCV risk behaviours but the effect on HCV transmission itself was not evaluated(2). Another study among PWID compared two types of counselling but there was no comparator arm without a counselling intervention, so the effect of counselling on transmission could not be analysed(376).

2.6.4. Community transmission prevention initiatives

Large scale attempts to prevent community transmission of HCV have come through regulatory requirements such as those requiring disinfectant for equipment used in nail salons, tattoo parlours, and barbershops in the US(22, 412). However, the impact of the introduction of these regulations has not been studied. One study in New York City, USA, has looked at an intervention to increase the knowledge of HCV transmission among people

working in barberships and hair salons(213). The intervention increased HCV transmission knowledge but the effect on HCV transmission itself was not evaluated(213).

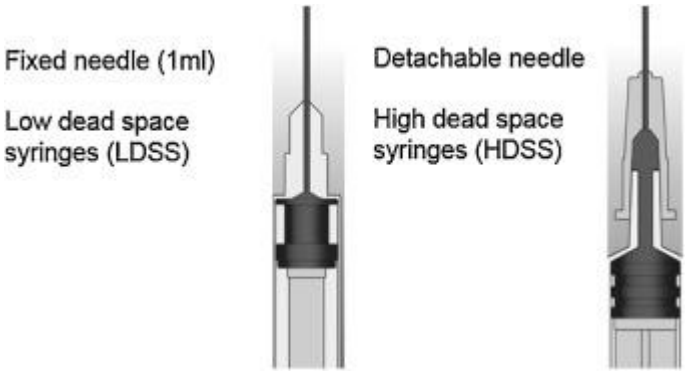
2.6.5. Needle and syringe provision for people who inject drugs

The purpose of needle and syringe provision (NSP), or needle and syringe programmes (NSPs), is to reduce the transmission of blood-borne viruses by providing clean needles and syringes to PWID so reducing their need to re-use or share needle/syringes(212). NSPs are often also providers of HCV testing as well as safe injecting advice(212). A recent systematic review and meta-analysis did not find evidence that NSPs are associated with reduced HCV acquisition risk(288). However, the same review did find that high-coverage NSP was associated with a reduced risk of HCV acquisition among PWID in Europe, around 56%, but this was not seen in North America(288). Global NSP coverage is low, with a review published in 2017 estimating there are just 93 countries with NSPs and only nine provide the WHO's recommended 200 clean needles and syringes per PWID annually(209).

2.6.6. Low dead space syringes

Syringes with attached needles usually have a lower 'dead space' than those with detachable needles(424), as illustrated by figure 2.1. These syringes with attached needles, also known as low dead space syringes (LDSS), retain much less blood after an injection compared with detachable needle syringes (or high dead space syringes [HDSS])(39). A syringe's volume of blood predicts the survival of the virus outside of the body and the viral load transmitted(1). A study in North Carolina, USA, found an increased prevalence of HCV with increased use of HDSS(425), although this finding was not replicated in a Hungarian study(133). A study in the UK found that the use of LDSS was associated with a 23% lower prevalence of HCV among PWID(372). This reduction was greater for those that had been injecting for less than three years, 47%(372). However, studies have so far been limited to examining associations with HCV prevalence, rather than incidence infections.

Figure 2.1: Illustrations of the dead space in low and high dead space syringes†.



† Artwork licensed by Creative Commons. Reproduced with permission from William Zule.

2.6.7. Opioid substitution therapy

To treat opioid dependence, drug users are given a replacement opioid, often methadone or buprenorphine(288), to reduce their frequency of injecting. This treatment for opioid dependence is usually known as opioid substitution therapy (OST) but can also be referred to as medication-assisted treatment (MAT)(221), or methadone maintenance treatment (MMT)(423). Globally, opioids are the drug of choice for around 82% of PWID(77). A recent systematic review found strong evidence that OST reduces the risk of HCV among opioid-dependent drug users, around a 50% reduction(288). However, a recent systematic review found that only 16% of PWID use OST, with just 86 countries having OST programs(209). High-income countries are more likely to have OST programs and are also more likely to have higher OST coverage than low- or middle-income countries(209).

2.6.8. Treatment as prevention

Treatment as prevention for HCV occurs when infections are averted through treating individuals that would otherwise transmit the virus to others(238). A study modelling across the whole infected population of Egypt, which consists of few PWID, found that 0.08-0.11 infections are averted per DAA treatment over 15 years(28). A study of Pakistan's infected population, which assumed an increasing epidemic, found around 0.56 infections are averted per treatment over 15 years(218). A modelling study with no set location found treating people that had never injected or were ex-injectors was found to avert no new

infections over a period of 50 years in one study(240). However, in the same study the number of infections averted per treatment among PWID varied from 0.2 to 2.3 depending on the chronic HCV prevalence among PWID and the disease stage(240). A UK study found that treating MSM with DAAs would give a reduction in HCV incidence of 1.3 infections per 100 person-years in 2025 compared with 2015(239). Various modelling studies have looked at HCV treatment as prevention among PWID(34, 70, 144, 238, 251, 421). Two studies found that treating PWID earlier in the course of disease progression would avert more infections(70, 144). A modelling study of PWID in the UK found 1.06 infections averted per PWID treated over a period of 12 years(34). A US study looked at the effect of injecting networks and found, in terms of treatment as prevention, that when DAA treatment coverage is high, selecting individuals at random was preferable to selecting PWID with the most injecting contacts(421). My study, described in detail in chapter 8, found that globally 0.35 infections were averted over 20 years per randomly allocated DAA treatment, which varied by region and country(373). The preventative impact of treating PWID also varied by country and region, with around 1.27 infections averted per treatment, globally(373).

2.7. HCV prevalence and genotype distributions by region

2.7.1. Introduction

Globally, it is estimated that around 71.1 (95% uncertainty interval: 62.5-79.4) million people are chronically infected with HCV, giving a global prevalence of around 1%(40). Assuming a viraemic rate of 76%(252) this would give an anti-HCV positive prevalence estimate of about 1.3%. The chronic prevalence of HCV varies both by region and by countries within regions(40). The region with the highest is Central Asia, at around 3.6%, whilst Latin America and Western Europe have the lowest estimated prevalences of around 0.5%(40). Despite having lower prevalences than the global average, South Asia and East Asia contain the largest number of infected individuals, around 15.3 and 10.5 million people, respectively, driven by large populations(40). A recent modelling study estimated Gabon, Mongolia, and Egypt are the countries with the highest chronic prevalences at 7.0%, 6.4%, and 6.3%, respectively, whilst the Netherlands has the lowest prevalence of around 0.1%(40). Globally, genotype 1 is the most common genotype, affecting almost half of infected individuals. However, genotypes and subtypes vary by region, with genotype 3 being the second most

prevalent overall and genotype 4 being the most prevalent in Africa and the Middle East(285).

2.7.2. HCV prevalence

At the time of writing, the most widely used estimate of 71.1 million people living with chronic HCV worldwide is taken from a 2017 paper by Blach et al – the Polaris Observatory HCV Collaborators(40). The WHO cites this estimate in their official figures regarding hepatitis(407). This estimate was produced using data from a systematic review of anti-HCV prevalence to parameterise models fitted for 100 countries to calculate the number of people with chronic HCV in 2015. Model inputs and extrapolations used for countries without data were discussed by experts in each country. The analysis used anti-HCV prevalence data and multiplied this by viraemic rates. To produce the 2015 estimates from data that were mostly taken from years pre-dating this, information on the number of people cured, mortality, and HCV incidence were incorporated into the model to track how the epidemics changed over time. The number of people cured of HCV was calculated based on a combination of factors, including the number of treatments given and the sustained viral response rates, estimated from available data, as was information on liver-related mortality. A limitation of this estimation method is that HCV incidence estimates were produced by back calculation techniques due to a lack of available data. This involved mapping back incidence curves based on known risk factors in discussion with the country experts. For the countries with two or more prevalence studies, namely USA(15, 78, 158), France(85, 249), and Egypt(93, 181), the annual incidence was calculated using the difference in prevalences and time periods between the two studies. However, for most countries the historical shape of the epidemic had to be estimated through discussions with a panel of experts, who used incidence data on acute infections where and when available.

In general, in most settings there is considerable uncertainty in how HCV prevalence is changing over time due to a lack of multiple, comparable, robust, national-level general population surveys. Studies on HCV risk factors indicate that in recent years there has been better screening of donated blood(291) and less re-use of medical injections(283), two of the main risk factors for HCV transmission. This should have resulted in decreasing HCV transmission in many settings. Increasingly successful HCV treatment should also aid

decreasing these epidemics(104). However, the degree to which unsafe use of injecting equipment amongst PWID contributes to HCV epidemics is unclear and there is a lack of information about how its contribution is evolving(77). In certain settings, particularly the USA(330), there is evidence that HCV incidence is increasing(330). Additionally, in countries where much of the HCV incidence is due to IDU(16), general population surveys may underestimate HCV prevalence by not well sampling PWID because many are homeless or incarcerated(197). HCV prevalence studies often have many other limitations including small sample sizes, not being from recent years, and a lack of generalisability to the population of that country. This could be due to sampling from high or low prevalence regions or focusing on specific risk groups. Many studies only have data on prevalence of individuals with anti-HCV positive tests, rather than HCV RNA positivity. For comparability across studies, countries, and regions, sections 2.7.2.1 to 2.7.2.10 will focus on anti-HCV prevalence by region, as these studies are more widely available than those for HCV RNA.

2.7.2.1. Western Europe

Most countries in Western Europe have a lower anti-HCV prevalence than the 2015 global average of 1.3%, with an estimated regional average of around 0.7%(40). Data coverage for the region is excellent, with only countries comprising a very small percentage of Western Europe's population, such as Andorra and Greenland, lacking anti-HCV prevalence data(40, 124, 160). Countries towards the south, such as Greece, 1.8%(40), Italy, 2.4%(40), and Spain, 1.7%(124), tend to have higher reported anti-HCV prevalences, whilst countries in the north such as Finland, 0.5%(40), Germany, 0.6%(40), and the UK, 0.5%(40), generally have the lowest prevalences in the region. France is one of only three countries globally to have two national surveys using similar methodology, allowing comparison over time(85, 249). These two surveys show a decreasing prevalence between 1994 and 2004, from 1.1%(85) to 0.8%(249). The data underlying Greece's estimated prevalence is also considered high quality based on the generalisability of the sample, the sample size, and the recency of the estimate. Eight other Western European countries have estimates rated as worse than this but are still considered to be moderate(40). As with other high-income countries and regions, the anti-HCV positive population in Western Europe is mostly comprised of people who have injected drugs and people that received a contaminated blood transfusion before

blood screening was introduced in the early 1990s(267). As people infected with contaminated blood transfusions are dying due to old age and liver-related causes, people who have injected drugs comprise an increasing proportion of the prevalent HCV infections(267). The estimate for the proportion of adults that are PWID in Western Europe, 0.34%, is around the global average of 0.33%(77). HCV incidence among PWID in most countries in Western Europe is still high(267). Emerging epidemics have also been seen among MSM(135, 290), and in some countries migrants from high-prevalence countries account for most of the prevalent infections(267, 385).

2.7.2.2. Eastern and Central Europe

For both Central and Eastern Europe, data coverage is excellent, with estimates available for all countries(40, 124, 160). In Central Europe, most countries have anti-HCV prevalences around the global average, whilst in Eastern Europe anti-HCV prevalences are among the highest in the world(40). Moldova has the highest estimated anti-HCV prevalence in Eastern Europe, 4.5%(124), followed by Russia at 4.1%(40). Russia is Eastern Europe's most populous country and comprises much of its burden. Belarus has the lowest anti-HCV prevalence in Eastern Europe at 1.3%, whilst all other countries have prevalences higher than the global average(124). For Central Europe, Romania has the highest anti-HCV prevalence estimate of 3.2%(40), whilst Albania's estimate, 3.0%(160), is also high. However, prevalence estimates for other countries such as Slovakia (1.4%)(40), Poland (0.9%)(40), and Bosnia (0.1%)(160), are much lower. Romania and Slovakia's prevalence estimates are considered high quality, whilst several other countries in the region have moderate quality data(40). Similarly to Western Europe, the HCV-positive population of Eastern and Central Europe mostly comprises PWID, former injectors, and people previously infected through blood transfusions(267). However, Central Europe and Eastern Europe have much higher proportions of adults that are PWID than Western Europe, with Eastern Europe having the highest globally, 1.30%, resulting in larger populations with high infection rates(77).

2.7.2.3. Australasia and Oceania

Australia (1.3%)(40), and New Zealand (1.4%)(40), both have average anti-HCV prevalence estimates. In Oceania, data coverage is poor with estimates unavailable for most of the Pacific Island countries, with Fiji and Samoa the exceptions(40). Fiji, with 0.1%, and Samoa, with 0.2%, have two of the lowest anti-HCV prevalence estimates in the world(40). Australia and Samoa have moderate quality estimates, whilst those for Fiji and New Zealand are poor(40). Australia and New Zealand have epidemic characteristics similar to those seen in other high-income countries(82, 113), whereas the epidemics in Oceania have been studied little and IDU is not very prevalent so HCV transmission in the region is not well understood(145).

2.7.2.4. East and Southeast Asia

The anti-HCV prevalence estimates for countries in East and Southeast Asia are generally lower than the global average(40, 124). However, due to the huge amount of people living in this region, a large proportion of the world's anti-HCV infected population are located here(40). Anti-HCV prevalence estimates are available for most of the region's countries(40). The country with the highest prevalence in the region is Cambodia with an estimate of 5.8%(40), followed by Taiwan (3.3%)(40), and Papua New Guinea (2.2%)(40). The majority of countries in the region have middling or low anti-HCV prevalences, such as 1.2% in China(40), 1.0% in Japan(40), and 0.8% in Indonesia(40). Most of the region's countries have moderate quality data estimates, whilst Indonesia and Papua New Guinea's estimates are considered high quality(40). East and Southeast Asia comprises a diverse range of countries, with the high-income countries, such as Japan, having similar epidemics to those in other high-income countries(333, 415). However, lower-income countries, such as Papua New Guinea, likely have higher levels of ongoing medical transmission due to less robust blood screening and sterilisation practices(145). The proportion of adults that are PWID in the region, 0.25%, is lower than the global average(77) but IDU is still an important source of HCV transmission(387).

2.7.2.5. South Asia

Data coverage is quite good for South Asia(40, 124). For all countries in the region except Pakistan (4.8%)(40), prevalence estimates are low(124). For example, 1.3% in Bangladesh (1.3%)(124), 0.8% in India (0.8%)(40, 121), and 1.1% in Afghanistan (1.1%)(40). Due to the huge population sizes in the region, combined with the high prevalence in Pakistan, South Asia is the region with the highest number of HCV infected people(40). The data estimate from Pakistan is considered high quality, whilst that of Afghanistan is moderate, and Bangladesh's estimate is poor(40, 124). For India the overall estimate is also poor quality(40). India is a huge country in both size and population, and while some areas have very high-quality data, most have almost none(121). There is also high heterogeneity in anti-HCV prevalences across the regions of India, varying from 3.6% in Punjab, to almost 0.0% in Maharashtra(121). South Asia is the region with the lowest proportion of adults that are PWID, 0.09%(77). Iatrogenic HCV transmission in the region is thought to be high and community transmission could also be a factor(333). Pakistan's particularly high prevalence, which will be discussed in-depth in chapter 4, is probably driven by very high rates of medical syringe re-use(371).

2.7.2.6. Central Asia

The countries in Central Asia have the world's highest anti-HCV prevalence estimates(40). Robust prevalence estimates are available for all the region's countries except Armenia(40, 124, 160). The region's highest anti-HCV prevalences estimates have been found in Uzbekistan (13.1%)(40), Mongolia (9.8%)(40), and Georgia (7.7%)(40). The prevalence estimates for all the region's other countries are lower than these but still far higher than the global average – for example, Turkmenistan, 5.6%(124), Azerbaijan, 3.7%(40), and Kazakhstan, 3.2%(40). Georgia and Mongolia have high quality data, whilst the data from Azerbaijan, Kazakhstan, and Uzbekistan are moderate(40). In Central Asia the proportion of adults that are PWID is high, 0.63%(77). The Georgian HCV epidemic, in particular, has been driven by IDU(132), where in 2004 4.2% of adults were PWID - the highest estimated injecting prevalence in the world(77). However, iatrogenic transmission was likely a major contributor to the high HCV prevalences seen in the region's other countries, as well as community transmission(30, 204).

2.7.2.7. Middle East and North Africa

Availability of data for prevalence estimates across the Middle East and North Africa is excellent(40). Most countries in the Middle East and North Africa have anti-HCV prevalence estimates lower than or around the global average(40), for example, Saudi Arabia, 0.5%(40), Iraq, 0.4%(40), Libya, 1.2%(40), and Turkey, 1.0%(40). Some countries have higher estimates such as Israel, 2.0%(40), Syria, 2.8%(40), and Egypt, which has a much higher prevalence(181). Egypt is one of the few countries in the world with two robust national studies that use similar methodology so are comparable over time. The first of these studies in 2008 found an anti-HCV prevalence of 14.7%(93), whilst the 2015 study found the prevalence had decreased to 10.0%(181). Turkey, Syria, Libya, and, Iraq all have prevalence estimates considered high quality(40). However, the estimates for Syria, Libya, and Iraq all pre-date the wars in those countries(40). The estimates for most of the remaining countries are considered to be moderate quality(40). The major historical transmission route across the region is iatrogenic transmission, such as that seen in Egypt, with community transmission also a possible, lesser, contributor to the epidemic(58). IDU in the region is rare – 0.12% of adults are PWID(77).

2.7.2.8. Sub-Saharan Africa

Data availability is quite good for anti-HCV prevalence estimates across the countries of Sub-Saharan Africa(40, 309), but most available estimates are considered poor quality(40, 124, 309). Data quality is high for the estimates from Burundi and Central African Republic(40) and eight countries have moderate quality estimates(40). However, the estimates for the remaining countries in the region, the vast majority, are poor(40, 124, 309). There is high heterogeneity in the prevalence estimates across Sub-Saharan African and the sub-regions within(40, 309). In Southern Africa, Angola has the highest prevalence with 3.9%(309), whilst other estimates range from 1.1% in Botswana(309) to 1.7% in South Africa(40). In East Africa the lowest anti-HCV prevalences estimate is found in Kenya (0.8%)(40). However, most anti-HCV prevalence estimates are close to the global average or higher, such as in Madagascar (1.2%)(40) or Tanzania (2.7%)(309). For West Africa, Gambia (0.5%)(40) has the lowest anti-HCV prevalence but, where available, most prevalences estimates are high, such as 2.1% in Ghana(40), and 3.5% in Burkina Faso(40). Nigeria, the

most populous nation in Africa, also has a high prevalence of 2.2%(40). In Central Africa prevalence estimates tend to be high, except for Central African Republic (0.6%)(40). Gabon, at 11.2%(40), has the highest prevalence estimate in Central Africa followed by 8.2% in Burundi(40). Estimates for the remaining countries in Central Africa vary from 2.0% in Chad(40) to 4.3% in the Democratic Republic of Congo(124, 309). Most of the historic transmission in the region is iatrogenic, particularly through unscreened blood transfusions(342). Although blood screening in the region has improved over the last two decades, high-quality screening is not universal across the region, meaning that iatrogenic HCV transmission is likely ongoing and is the major contributor to incidence(342). However, transmission via community risks and IDU could also contribute to the epidemic(342), although the prevalence of adults that are PWID is low, 0.28%(77).

2.7.2.9. North America

The anti-HCV estimates available for Canada and the USA are moderate and high-quality, respectively(40, 78, 158). Canada's estimated anti-HCV prevalence is 1.0%, which is lower than the global average(40). The USA has had several national studies of HCV prevalence that use similar methods making them comparable over time(15, 78, 158). The first of these US estimates (1988-1994) gave an anti-HCV prevalence of 1.8%(15). The next estimate showed a decrease, giving a prevalence of 1.3% for 2003-2010(78). The latest, very recently published, estimate showed an anti-HCV prevalence increase to 1.5% for 2013-2016(158). When additionally including incarcerated, military, homeless, and nursing home populations into this estimate it rises to 1.7%(158). Other data suggest a recent increase in HCV infections in the USA due to a rising epidemic of IDU (330). Otherwise, HCV transmission in North America has likely followed a similar pattern to other high-income countries and regions(260, 330).

2.7.2.10. Latin America and the Caribbean

Both Latin America and the Caribbean have poor coverage of anti-HCV prevalence estimates(40). Coverage is particularly bad for the Caribbean and Central America, whilst it is better in South America(40). All the available estimates for countries in the region are

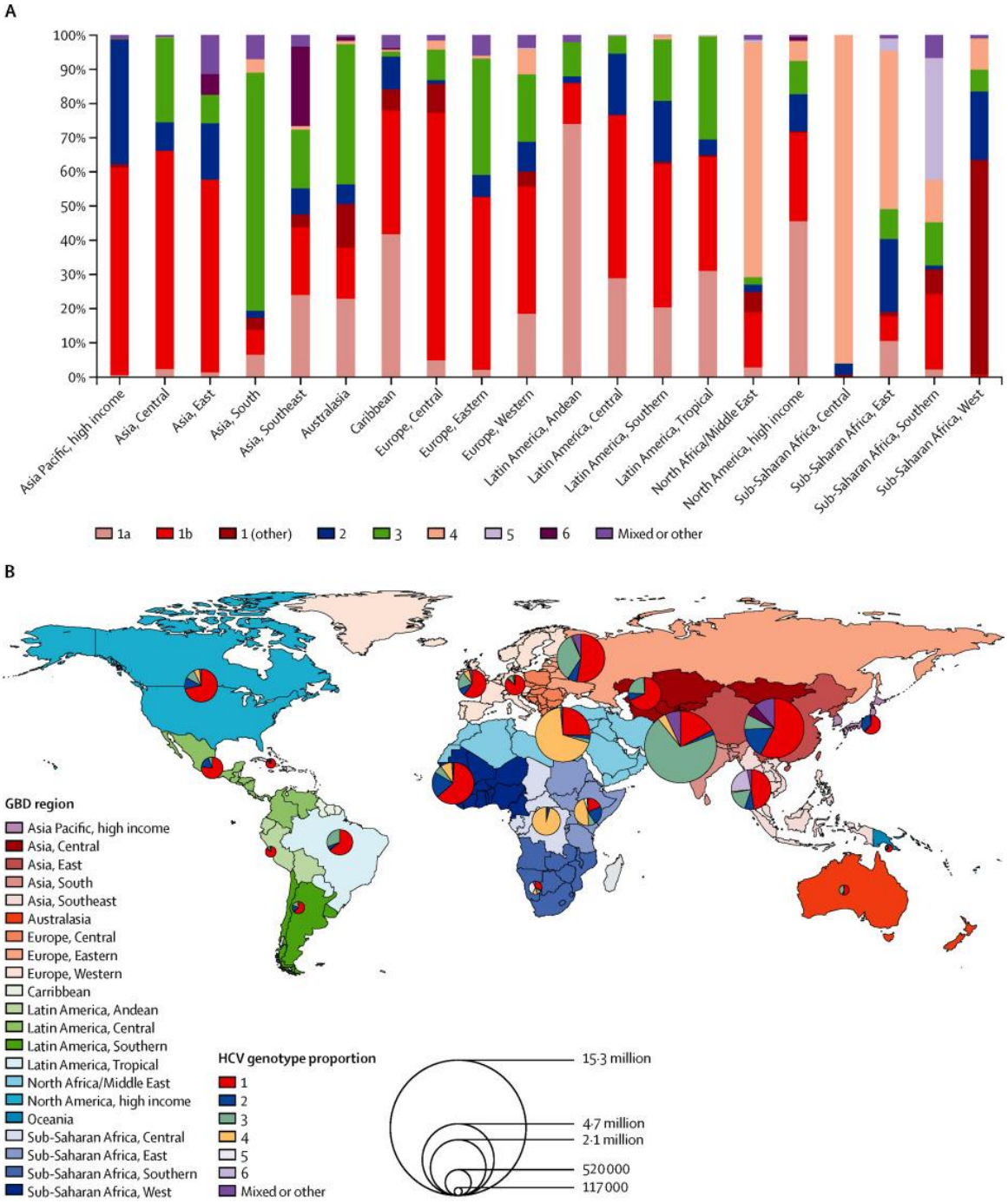
either around the global average, or in most cases, lower(40). Argentina has the highest estimated anti-HCV prevalence in the region, 1.5%(40). Brazil and Mexico, the two most populous countries in the region, have the next highest prevalences with 1.4%(40). Prevalences are lower for other countries such as Chile, 0.8%(40), the Dominican Republic, 1.0%(40), and Panama, 0.5%(40). Brazil and Mexico have high quality data, whilst Chile's is considered moderate(40). However, the other countries have poor data, with expert consensus used to derive the estimates for the Dominican Republic and Panama(40). Epidemiological studies in the countries of Latin America indicate that the major route of transmission has been iatrogenic although this is decreasing with improved blood screening(375). High HCV prevalences have been found among PWID in various Latin American countries and IDU is now thought to be the primary risk factor for transmission(354). There has been a lack of research into HCV in the Caribbean and as such the epidemic there is poorly characterised.

2.7.3. HCV genotype distributions

The distribution of HCV genotype distributions was previously considered very important due to the differing effectiveness of treatment by genotype, but there is less interest following the development of pan-genotypic treatments. Globally, the prevalence of HCV genotype 1 among infected individuals is just under half(40, 250, 285), whilst genotype 3 is the second most prevalent, with estimates ranging from 18% to 30%(250, 285). Genotypes 4 and 2 are the next most common, with varying estimates of 8.3%-16.8% and 9.1%-11.0%, respectively(250, 285). Worldwide, genotypes 5, 6, and particularly 7, have low prevalence(40, 250, 285). The prevalence of genotype 1 varies regionally from the vast majority of all infections in parts of Latin America and the Caribbean, to just less than 20% in Central Sub-Saharan Africa, and South Asia, see figure 2.2(40, 285). For South Asia most infected individuals have HCV genotype 3(40). The most common genotype in Central Sub-Saharan Africa is genotype 4, as is the case for North Africa and the Middle East(285). In South Sub-Saharan Africa genotype 5 is the most common, comprising roughly 36% of infections(285). There is debate about the most common genotype in West Sub-Saharan Africa, with some evidence suggesting genotype 2 is the most common(285), whilst other information suggests genotype 1 is dominant(40, 250). Regional variations in genotype distributions are influenced by human migration patterns, and the route of

transmission(233). Subtypes 1a, 1b, 2a, 2b, and 3a are found worldwide and constitute most of the HCV infected individuals(389). It is thought that these subtypes were mostly spread before the era of HCV testing via blood transfusion and IDU, particularly in high-income countries(339). The other genotypes and subtypes are rarer and are more isolated geographically to Africa and Asia(285).

Figure 2.2: Genotype distribution by GBD region (A) and HCV genotype and total infected by GBD region (B).



GBD: Global Burden of Disease.

Reprinted from the article *Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study(40).*

CHAPTER 3. A BACKGROUND TO MATHEMATICAL MODELLING OF HEPATITIS C VIRUS EPIDEMICS

3.1. Introduction

Mathematical modelling can be used to understand how infectious diseases are spread, what causes the epidemic, and how an epidemic will evolve in the future(186). Models can also be used to investigate how transmission can be prevented, the effect of interventions and other factors on an epidemic, and the cost-effectiveness of such interventions(186). Mathematical models have advanced a lot since their first recorded use when in 1760 Daniel Bernoulli modelled smallpox showing that healthy people could be effectively inoculated(38). Since then the computational power available has developed massively, as have the complexity of mathematical models(215). Today's models can be important for policy making around infectious diseases(200). For example, the WHO changed its guidelines to state that all people should start antiretroviral treatment upon being diagnosed with HIV regardless of CD4 cell count/μL partly based on the use of mathematical modelling(89, 141, 396). For HCV, there are also examples of mathematical modelling being used to guide policy making, however, with governments also starting to engage with modellers for planning the development of their treatment programs(149, 218). This chapter will explain how mathematical models of infectious diseases can be categorised, static or dynamic, deterministic or stochastic, compartmental or individual based, and what these categorisations mean and when they should be used. Following this, an example of a basic model will be given, before the chapter concludes with examples of the mathematical modelling of HCV.

3.2. Static or dynamic models

One of the categorisations of mathematical models is whether they are static or dynamic(286). In static models, the rate of infection is pre-specified and does not depend on

the number of infected people that are modelled. For dynamic models, the infection rate depends on how many people are infectious. For example, in a dynamic model if the prevalence of HCV among people who inject drugs (PWID) is very high and is then reduced through treatment, this can reduce the risk of infections among those not infected because there are less infected people to transmit the virus. Alternatively, this can also increase the incidence rate as there are more people available to be infected. In a static model, this is not the case. A static model could be an appropriate choice of model when the population subgroup that is the target of an intervention does not contribute much to transmission, for example people who were infected with HCV through contaminated blood transfusions decades ago, that are not injecting drug users, are unlikely to transmit the virus to others. However, in many circumstances the intervention being investigated will impact on the dynamics of transmission, such as the creation of a herd immunity effect(46) where vaccines additionally benefit the unvaccinated when vaccine coverage is high; in such cases the use of dynamic models is crucial(286).

3.3. Deterministic or stochastic models

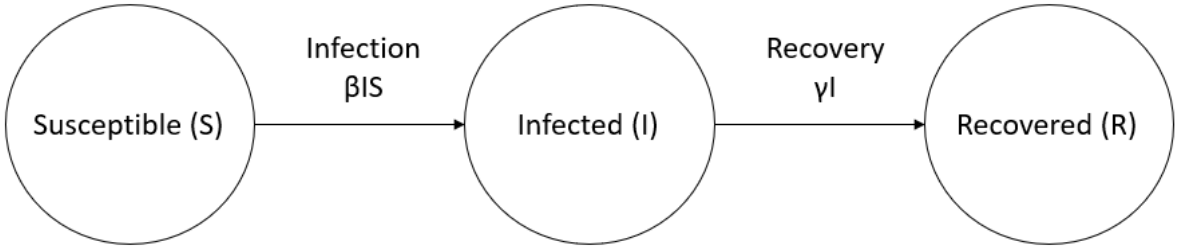
A second categorisation of interest for mathematical models is between deterministic and stochastic models(286). Usually deterministic models are at the population-level, with the population divided into different states or compartments, for example, susceptible, infected, and recovered, and the number of individuals in each state changes over time. Deterministic models are usually defined by sets of differential equations (or difference equations) that correspond to the rates of population movement through the various states(286). Meanwhile, stochastic models are usually designed at the individual-level and probability distributions describe the transitions between the available model states(286). As a system of equations, if a deterministic model is run multiple times with exactly the same model inputs then each run will produce identical results(286). Whereas, the probability distributions in stochastic models include chance (stochasticity) that means the possibility of variation between any two runs produced with the same model inputs(286). Stochastic models can also capture individual variation in population behaviours, whereas in deterministic models individuals are allotted into groups and assigned average levels of behaviours. As such, stochastic models are often thought to be more realistic(269). Deterministic models are appropriate for modelling established epidemics with a large number of infected

individuals, where the average of the variability produced by the probability distributions of the stochastic models approximates the transmission dynamics of deterministic models(286). Although considered more realistic than deterministic models, due to their complexity, stochastic models take longer to compute and can be much harder to parameterise as they are usually at the individual-level(70, 186, 269). Network models are another form of stochastic models where a contact network of individuals is designed through which transmission can occur(72). These network models require specific data on contact patterns between individuals, which can be difficult to obtain(72). Deterministic models are parameterised using population-level rates that, where unavailable, can often be produced through calibration to an observed prevalence. Whilst stochastic models incorporate chance through their stochasticity, the role of uncertainty can, and should, be added to deterministic models though the sampling of input parameters from probability distributions such as 95% confidence intervals(45). This addition of uncertainty across the input model parameters can result in very different outputs using the same deterministic model structure. Therefore, the role of this uncertainty can be important, for all model types, and analyses should be performed to investigate how much it effects the model outputs and which parameters are particularly influential(45).

3.4. Susceptible, Infected, Recovered model example

The first paper on the Susceptible, Infected, Recovered (SIR) model was published by Kermack and McKendrick in 1927 and forms the basis of deterministic mathematical models(189). The SIR model is one of the simplest compartmental models from which other more complicated models can be derived. I will use the SIR model here to give an example of how deterministic models can work. In an SIR model the population is split into three states (or compartments): Susceptible, Infected, and Recovered. The number of individuals in each of these states at time t is given by $S(t)$, $I(t)$, and $R(t)$, respectively. Those in the Susceptible state have never been infected and are susceptible to infection, whilst those in the Infected state are currently infected, and the population in the Recovered state are individuals that have recovered from the infection and are immune to being reinfected. This model assumes that as soon as a person is infected, they are infectious to others and that they remain infectious for the entire duration of that infection.

Figure 3.1: SIR model schematic featuring no births or deaths.



Individuals in the susceptible state (S) become infected at a rate β, multiplied by the number of infected individuals (I). This infection rate is denoted as βIS in the model, which is all of these terms multiplied together. Following infection, individuals enter the Recovered state at rate γ, which can be approximated by one divided by the duration of the infection if a negative exponential distribution of duration is assumed. This very basic SIR model does not include births or deaths; however, these can be easily added to the model. Figure 3.1 shows a schematic of this SIR model. This model assumes that the population is perfectly mixed, so that every susceptible individual can be infected by any infected individual. If every infected individual in the model has κ contacts per a given unit time, independent of the total population size ($N = S + I + R$), and a proportion of these contacts, α, results in a transmission of the disease, then each infected individual has $\frac{\kappa S}{N}$ contacts with susceptible individuals per unit time. Subsequently, $\frac{\alpha\kappa S}{N}$ susceptible individuals are infected by each infected individual per unit time, which when multiplied by the number of infected individuals, gives $\frac{\alpha\kappa IS}{N}$. This is the total number of infections per unit time and, therefore, the transmission rate β can be defined $\beta = \frac{\alpha\kappa}{N}$. The model equations are shown below:

$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

This SIR model can be further adapted to include more states that better represent the transmission dynamics and natural history of particular infectious diseases. For example, upon being infected with tuberculosis, individuals are not infectious for a specific period of time known as the latent stage, which is often denoted as an exposed state (E). This state can

be added to the basic SIR model to form an SEIR model. Conversely, for models of infections where recovery does not give immunity to reinfection, individuals could transfer back to the Susceptible state (*S*), from which there is a probability of reinfection, such as for chlamydia. Such a model would not include the Recovered state (*R*) and is known as an SIS model. There is no limit on the number of states that can be used to model the natural history of a disease, nor is there a restriction on the number of different types of states that can be included. Other examples of compartments are carrier states, or a state of partial immunity after recovering from an infection. States that differentiate between disease severity can be included, which is common for modelling of HCV to separate those chronically infected from individuals with cirrhosis. Additionally, intervention states can be included, such as treatment or vaccination compartments, which can alter the dynamics of transmission. The model population can be stratified into subgroups with differing transmission rates or patterns of mixing, such as by gender, age, or disease risk groups. In such examples, it can be assumed that individuals are more likely to have contacts with other individuals from their own risk group, known as assortative or like-with-like mixing. Random mixing can also be assumed where the number of individuals in each risk group determines the distribution of contacts an infected individual has with susceptible individuals from another risk group. The design and assumptions of each model used should be specific to that disease and the questions being asked.

3.5. Examples of mathematical modelling of HCV epidemics

Mathematical modelling of HCV epidemics has taken various forms depending on the aims of those designing the models. These include models investigating the viral kinetics of HCV infection(59, 71), as well as models of HCV burden(40, 150, 218), HCV transmission(152, 421), and cost-effectiveness models(62, 237). Viral kinetic models look at how HCV infections evolve within a person, whereas the other models are at individual- or population-level and are more relevant to this thesis, particularly those looking at HCV burden.

Models of HCV burden have been designed for various settings, including communities(110) and countries(28, 40, 162), and for different populations, such as PWID(90, 109), MSM(241, 317), prisoners(237, 349), and the general population(218, 299). Much of the

modelling of national HCV burden has been deterministic, but not dynamic, in the form of Markov models(40, 301, 308). Due to the lack of data on HCV incidence, for Markov models this parameter has to be pre-specified, which for most national models has been done through back-calculation and in some cases expert opinion(40, 217, 332), considered the poorest type of evidence(416). Many of the models of HCV burden that have used dynamic modelling have been able to estimate the incidence by calibrating to one or more HCV prevalence estimates(70, 110, 150). As HCV epidemics in most subgroups of interest, such as PWID or the general population, are well established, deterministic models are generally used rather than stochastic models, which are more suitable for modelling the initial spread of an epidemic(323).

Whilst burden models generally include a component of HCV transmission through an incidence rate, network models have tended to give the most detailed investigations of HCV transmission(70, 251). Network models, a form of stochastic model, require in depth information about the contact structure of each member of the network, which can be very difficult and time-consuming data to gather, particularly for large scale modelling exercises(112). In HCV research, these network models have been used most commonly for epidemics among PWID where the route of transmission is most likely due to injecting drug use and the transmission dynamics can be modelled through drawing a picture of the contacts between PWID. Network models are less suited to generalised epidemics where transmission could occur through various routes, including blood transfusions, making it very difficult to model using a network. PWID network HCV models have looked at the effect of treatment as prevention through targeting different members of the network and how this differs with varying treatment coverage and HCV prevalence(152, 251, 421). Zelenev et al. found that targeting PWID with the most contacts is the best strategy when treatment coverage is low but there is less difference between who is targeted with higher treatment coverage levels(421).

Cost-effectiveness studies of HCV have mostly modelled the benefits in terms of morbidity or mortality averted per HCV treatment, either considering interferon-based regimens or DAAs(62). A review of HCV cost-effectiveness studies published in 2015 found that all of the studies included were from high-income countries and all used static modelling techniques rather than dynamic models(62). Consequently, none of these models could account for prevention benefits in terms of infections averted and therefore may have

underestimated the benefits of HCV treatment(62). Since that 2015 review (and before), other HCV cost-effectiveness studies have been published with dynamic structures(235, 382). Additionally, some studies have also investigated the cost-effectiveness of HCV case-finding or screening(26, 237).

Aside from those looking at the cost-effectiveness of case-finding and screening, studies on HCV have also modelled the role of case-finding and screening in the HCV treatment cascade(302). Models investigating screening have tended to be deterministic, including a compartment or compartments for diagnosis(150, 370), although decision tree modelling has also been used to assign probabilities of HCV-infected individuals linking to care(26). HCV screening models have mostly investigated assumptions around numbers of diagnoses needed for treatment targets and the yield of screening in different settings or among different subgroups(237).

CHAPTER 4. IMPORTANCE AND CONTRIBUTION OF COMMUNITY, SOCIAL, AND HEALTHCARE RISK FACTORS FOR HEPATITIS C VIRUS INFECTION IN PAKISTAN

The work in this chapter was done in collaboration with Margaret T May, Charlotte Davies, Huma Qureshi, Saeed Hamid, Hassan Mahmood, Quaid Saeed, Matthew Hickman, Nancy Glass, Francisco Averhoff, and Peter Vickerman, and is published in the American Journal of Hygiene and Tropical Medicine(371).

4.1. Introduction

The prevalence of the population with hepatitis C virus (HCV) antibodies in most countries is low (<1%), but has been estimated to exceed 4% in at least 12 countries including Egypt, Georgia, and Pakistan(124, 295, 352), where the interest in reducing HCV transmission has been particularly high(56, 132). It is crucial to tackle the underlying risk factors that drive HCV transmission in order to reduce it. Additionally, to effectively scale-up treatment it is important to understand how to optimally target HCV testing interventions to minimise costs. This is especially true for countries with such a large burden of HCV as Pakistan, which I focus on in this chapter. Pakistan is the fifth-most populous country in the world, with a population of around 208 million people in 2017(276), and a gross domestic product per capita of $5,374 (USD) in 2016 (the world average was $15,800)(168). In Pakistan there are an estimated 9 million infected individuals(295), however, healthcare expenditure only makes up 0.9% of GDP (compared to 10.0% across the EU and 17.1% in USA(364)). Understanding what risk factors and markers are predictive of HCV infection could inform efficient, targeted screening recommendations that could reduce costs and time.

Since 2005 a number of major hepatitis prevention and control programs in Pakistan(184, 186) have focused on ensuring safe blood transfusions, improving disposal of syringes, increasing public awareness, and educating healthcare professionals and barbers(202, 324, 325). However, the effectiveness of these interventions in reducing HCV transmission in

Pakistan is unknown. As part of this interest in tackling HCV, in 2007 a large (n=46,843) national sero-prevalence survey for HCV was carried out in Pakistan. It found an anti-HCV prevalence of 4.9% overall, 6.7% amongst adults (aged ≥16 years), which did not differ by sex(295). HCV infection prevalence was higher in the more populous Eastern provinces of Punjab (6.7%) and Sindh (5.0%), than in the less populated provinces of North West Frontier (1.5%) and Baluchistan (1.1%). Previous analyses using this dataset have only considered univariable associations with HCV sero-prevalence, therefore these associations did not account for the effects of other variables and were open to issues of confounding. Those previous analyses found that increasing age, being married, shaving, sharing a toothbrush, sharing smoking equipment, tattooing or acupuncture, ear or nose piercing, a history of surgery, a higher number of injections received, and re-using syringes for these injections were associated with a higher prevalence of HCV(295). They also found associations between HCV prevalence and socio-economic characteristics such as the type of housing, the source of water, sanitation source, education, and employment type.

In this chapter, I extend these previous unadjusted analyses by undertaking a multivariable analysis of the associations between exposures or risk factors and prevalent HCV infection. I investigate which of socio-economic, community, and medical risk reduction interventions are likely to be the most effective in reducing HCV acquisition in different populations defined by age, sex, and geographical location. This information is also useful for targeting testing, to know which risk factors are most predictive of HCV prevalence. I estimate the population attributable fraction (PAF) of HCV due to grouped community or healthcare exposures and risk factors. The PAF assesses the proportion of prevalent infections attributable to different exposures and depends both on the strength of association with HCV infection and the population prevalence of the risk factor. I also assess the cumulative effect of multiple exposures on lifetime risk of HCV.

4.2. Materials and methods

The serosurvey used in this chapter was designed previously by others. I performed all statistical analyses described in this chapter.

4.2.1. Description of the survey

The survey(295) was conducted in all four of Pakistan's provinces that are not classed as federally administered tribal areas or security-compromised areas (which account for roughly 3% of Pakistan's population). The survey was designed from enumeration blocks, the primary sampling units, of 200-250 households using the 1998 census survey, and a 2004 update for urban areas. For 14 large cities a separate structure was used that was divided into low-, middle-, and high-income groups. For the survey structure, urban areas were either considered part of these 14 cities or formed a separate group of all other urban areas. Urban and rural areas were considered separately, apart from in Balochistan which is too sparsely populated and so provincial administrative divisions were instead used as the stratifying unit. Households were drawn from 350 primary sampling units, 138 of which were urban and 212 rural. Included subjects gave consent to being tested. It was calculated that 7,000 households would be necessary for sampling. These households were sampled using a probability proportional to size method from with 3,500 drawn from Punjab province, 1,560 from Sindh, 1,100 from the North-Western Frontier Province, and 840 from Balochistan, with an average family size of 6.5 people. Appendix figures 4.1 and 4.2 show the household and individual survey questionnaires, respectively.

4.2.2. Demographic information

Age, sex, marital status (never married, married, divorced/separated/widowed), and the relationship with the survey responder were collected for all members of the household. Each person and household had a unique identifier and was labelled with the district and province. Age was grouped as 0-9, 10-19, 20-29, 30-39, 40-49, 50-59, and ≥60 years. The district was used to categorise households as urban or rural.

4.2.3. Outcome variable

Participants were only tested for antibodies to HCV (anti-HCV), not active infection. Sample testing for HCV was carried out using the rapid Advanced Quality One Step HCV Test (Bionike Inc.) system, which is estimated to have a sensitivity of 97.1% (95% confidence interval [CI]: 89.8–99.6%) and specificity of 96.3% (95% CI: 92.5–98.5%)(395). All further mentions of HCV in this chapter refer to anti-HCV.

4.2.4. Exposures and risk factors collected in the survey

Data were collected on whether participants had ever received haemodialysis, a blood transfusion, had a history of surgery, had a history of dental surgery, had a family history of hepatitis infection, practised matam (which ranges from ceremonial chest beating to self-flagellation with implements such as chains, and blades)(41, 66), visit a barber for shaving, shared a toothbrush, shared smoking equipment, had received either a tattoo or acupuncture, and had either an ear or nose piercing. The number of medical injections received in the last year (0, 1-4, 5-10, >10), and the type or syringe used (none, new disposable, re-used syringe, don't know) were recorded, as was whether they had a history of intravenous/injecting drug use. Occupation was dichotomised as labourer or not, education was dichotomised as illiterate or not.

4.2.5. Grouped exposures and risk factors

Risk factors and exposures that are surrogates for risk factors (for example, literacy as an indicator of socio-economic status) were grouped as socio-economic status, healthcare risk, and community risk exposures. Socio-economic status for all individuals was defined using data on the survey responder (assumed to be the head of the household). An individual was defined to have low socio-economic status if the head of the household was either a labourer or illiterate. Risk due to healthcare exposures was high if the person had previously had haemodialysis, a blood transfusion, or ≥5 injections in the last year. Lower numbers of yearly injections were not included as a healthcare risk exposure because 77% of the population reported at least one injection in the last year. Community exposures included going to the barber, sharing smoking equipment, having an ear or nose piercing, or having a

tattoo or acupuncture. For each of the healthcare and community grouped risk/exposure variables, I counted the number of exposures and categorised them as 0, 1, or ≥2 risk factors. I also counted the total cumulative number of exposures (0, 1, 2, 3, 4, or ≥5 risk factors).

4.2.6. Childbirth variable

I hypothesised that unsafe childbirth practices could be a risk factor for HCV acquisition in adult females. Although the survey did not directly ask respondents about their number of childbirths, it did list each household member and what their relationship was to the head of the household. Therefore, for females aged 20-59 years that described themselves as wife or head of household, and who identified themselves as married, the number of childbirths (0, 1, 2, 3, 4, ≥5 children) was estimated by counting the number of children in the household described as sons or daughters. I did not estimate number of childbirths for older females because of the increased likelihood that some of their children will have left home. Age was grouped as 20-29, 30-39, 40-49, and 50-59 years in this analysis.

4.2.7. Associations with HCV infection

4.2.7.1. Individual variable associations

I used logistic regression to estimate the unadjusted and mutually adjusted odds ratio (OR) (with 95% CI) for HCV infection for each individual exposure/risk factor. Separate models were estimated for each age group (0-19, 20-29, ≥30 years) and sex to see how associations varied across these groups. I also estimated the association of age with HCV prevalence by fitting separate models for males and females (for all age groups) that included age as a covariate. Robust standard errors accounted for clustering by household.

4.2.7.2. Grouped variable associations

To assess which of social, healthcare, or community interventions might have more impact on the risk of HCV, I grouped variables into these domains and re-estimated mutually adjusted sex-specific models which were also adjusted for province, age, and marital status

(referred to below as the "main analysis"). As the prevalence of HCV was much higher in the more populated provinces (Punjab and Sindh compared to Baluchistan and North-West Frontier), I performed sensitivity analyses of the main analysis looking at the grouped variables (i) without adjusting for province, (ii) omitting Baluchistan and North-west Frontier provinces.

A separate analysis was performed splitting the derived group variables into their individual components. I also investigated if the associations between the grouped variables and HCV infection varied by age as well as sex by repeating the main analysis separately for different age and sex combinations (male/female, age 0-19, 20-29, and ≥30 years old), adjusting for marital status, province, and further by age where appropriate. Community risk, medical risk, and socio-economic status risk were used as binary variables in this analysis (counting if participants had any of the individual factors associated risks or not).

4.2.7.3. Cumulative variable associations

The relationship between HCV prevalence and the total number of risk factor exposures was examined by fitting sex-specific models adjusted for age and province. Exposures included in this analysis were having ≥5 injections, haemodialysis, blood transfusions, going to the barber, ear/nose piercing, tattoo/acupuncture, sharing smoking equipment, marriage, illiteracy, and being a labourer.

4.2.8. Population attributable fractions

The population attributable fraction (PAF) (equation 4.1) was defined here as the proportional reduction in HCV prevalence that would occur if the risk factor were reduced to no exposure(207). I calculated this for each of the three risk factor domains. I also stratified the analysis by age and sex to observe whether the PAFs for each of the grouped variables differed by age as well as sex.

Equation 4.1: $\text{PAF} = \frac{P_e(RR-1)}{P_e(RR-1)+1}$

P_e = current prevalence of exposure (e.g. ≥5 medical injections)
RR = the adjusted relative risk of disease due to that specific exposure

4.2.9. Associations between HCV and childbirth

I investigated the importance of childbirth for HCV acquisition in wives aged 20-59 years, adjusting associations for age, province, socio-economic status, healthcare, and community risk. I did this among women that were categorised in the survey as wives, assuming only those who are married have children in Pakistan. This analysis was repeated stratifying the age-groups of the wives into a younger age-group, 20-29 years, and an older age-group, 30-59 years, to see if any associations between childbirths and HCV infection status differed based on age, possibly reflecting more recent improvements in healthcare. I then repeated this analysis in men aged 20-59 by assigning the childbirths of wives to their husbands, to see if childbirths themselves were associated with HCV (which would be the case if the number of childbirths were only associated with HCV in women), or if childbirths were a marker for low socio-economic status and possible poor healthcare, in which case an association would be seen in the husbands as well.

4.2.10. Association of re-use of syringes and socio-economic status

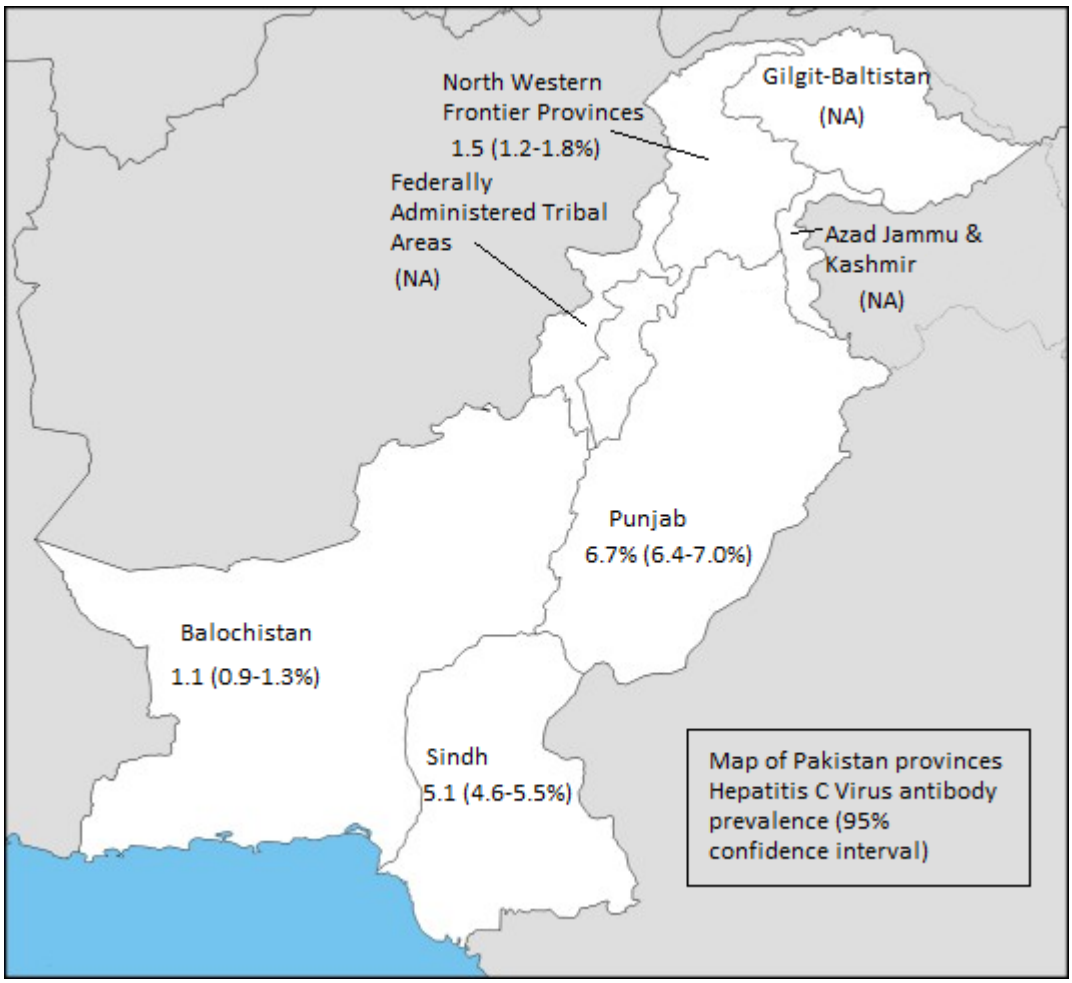
A study set in Pakistan found that socio-economic status was positively associated with the proportion of injections received using a new syringe, compared to re-use(177). To investigate whether this effect was evident in this dataset, logistic regression was performed with the outcome variable as whether or not the last syringe for a medical injection was re-used ("not" also included "don't know", and "no previous injection recorded"). The dependent variables included in this analysis were low socio-economic status (as a binary variable), age group (0-19, 20-29, 30-39, 40-49, 50-59, and ≥60 years), province, and sex, with clustering by household.

4.3. Results

4.3.1. Prevalence and study characteristics

Overall 46,843 people were included (96% of those sampled, with the 4% not tested because of migration, non-availability, or refusal) in the study and 2,290 [4.9% (95% CI: 4.7, 5.1%)] of the participants had HCV antibodies. The HCV prevalence was 4.8% (95% CI: 4.6, 5.1%) and 4.9% (95% CI: 4.7, 5.2%) for females and males, respectively. The prevalence of HCV was 6.7% (95% CI: 6.4, 7.0%), 5.1% (95% CI: 4.6, 5.5%), 1.1% (95% CI: 0.9, 1.3%), and 1.5% (95% CI: 1.2, 1.8%) in Punjab, Sindh, Baluchistan, and the North-west Frontier, respectively, which is shown in the map of Pakistan's regions in figure 4.1.

Figure 4.1: A map of the provinces of Pakistan, with the prevalence of HCV antibodies for each province.



4.3.2. Association of individual exposures and risk factors with HCV

Table 4.1 summarises the exposures associated with HCV stratified by age categories (0-19, 20-29, ≥30 years) and gender, which can be seen in further detail in table 4.2. Prevalence of exposures and association with HCV infection varied by age and gender. The prevalence of HCV infection was higher among married persons (both males and females) compared to those never married, and HCV prevalence increased with age and with the number of community and healthcare exposures. Only 0.1% of respondents said they had a history of injecting drug use and among these 14.0% were infected with HCV. In multivariable analyses injecting drug use was not associated with HCV for any of the groups split by age and gender. Exposures associated with increased odds of HCV among young males aged 0-19 years included, but were not limited to, visiting the barber [adjusted OR (aOR) 1.74 (95% CI: 1.09, 2.78)], re-use of syringes [aOR 1.52 (95% CI: 1.00, 2.31)], and having a family history of hepatitis infection [aOR 2.63 (95% CI: 1.34, 5.16)]. Among young females the risk factors included ear or nose piercing [aOR 1.59 (95% CI: 1.19, 2.13)], re-use of syringes [aOR 1.78 (95% CI: 1.19, 2.67)], being illiterate [aOR 1.62 (95% CI: 1.19, 2.21)], and having been tattooed or treated with acupuncture [aOR 13.8 (95% CI: 3.67, 51.5)], although very few (0.1%) reported tattoo or acupuncture. Females aged 20-29 had higher odds of HCV infection if they were married (versus single) [aOR 1.58 (95% CI: 1.15, 2.19)] or had ever received a blood transfusion [aOR 5.76 (95% CI: 1.73, 19.2)], however, numbers exposed to blood transfusions were small (1.3%). Males aged 20-29 were at higher risk of HCV if they reported haemodialysis [aOR 10.1 (95% CI: 1.19, 86.5)] or being a labourer [aOR 1.75 (95% CI: 1.18, 2.59)]. Females aged over 30 years had higher odds if they received haemodialysis [aOR 4.37 (95% CI: 1.61, 11.9)] or a blood transfusion [aOR 2.49 (95% CI: 1.55, 3.99)], whereas older males had higher odds if they were married [aOR 1.61 (95% CI: 1.15, 2.22)] or visit a barber [aOR 1.45 (95% CI: 1.24, 1.70)]. For both males and females aged over 30 years, illiteracy, being a labourer, a family history of hepatitis, and using a high number of syringes were all associated with increased odds of HCV infection, whilst there was a lower odds of HCV infection if the last medical injection they had received was re-used.

Table 4.1: Variables associated* with HCV infection, stratified by age category and gender, summarising tables 4.2a, 4.2b, and 4.2c.

Males	aOR (95% CI)	Females	aOR (95% CI)
Aged 0-19 years:			
Barber (vs not)	1.74 (1.09, 2.78)	Tattoo or acupuncture (vs not)	13.8 (3.67, 51.5)
Ear or nose piercing (vs not)	2.71 (1.47, 4.99)	Ear or nose piercing (vs not)	1.59 (1.19, 2.13)
Labourer (vs not)	1.99 (1.24, 3.21)	Illiterate (vs not)	1.62 (1.19, 2.21)
Re-used syringe (vs none/new)	1.52 (1.00, 2.31)	Re-used syringe (vs none/new)	1.78 (1.19, 2.67)
Family history of hepatitis (vs not)	2.63 (1.34, 5.16)		
Aged 20-29 years:			
Barber (vs not)	1.43 (1.01, 2.01)	Married (vs never)	1.58 (1.15, 2.19)
Labourer (vs not)	1.75 (1.18, 2.59)	Other marital status (vs never)	3.76 (1.07, 13.3)
Family history hepatitis (vs not)	2.83 (1.47, 5.43)	Barber (vs not)	4.22 (1.01, 17.6)
Haemodialysis	10.1 (1.19, 86.5)	Tattoo or acupuncture (vs not)	3.42 (1.05, 11.2)
		Ear or nose piercing (vs not)	2.30 (1.40, 3.76)
		Family history of hepatitis (vs not)	1.96 (1.09, 3.51)
		Blood transfusion (vs never)	5.76 (1.73, 19.2)
Aged ≥30 years:			
Married (vs never)	1.61 (1.16, 2.22)	Illiterate (vs not)	1.43 (1.15, 1.78)
Barber (vs not)	1.45 (1.24, 1.70)	Labourer (vs not)	2.05 (1.30, 3.23)
Illiterate (vs not)	1.30 (1.11, 1.52)	5-10 injections (vs 0)	1.65 (1.17, 2.33)
Labourer (vs not)	1.41 (1.18, 1.67)	>10 injections (vs 0)	1.92 (1.32, 2.79)
1-4 injections (vs 0)	1.69 (1.29, 2.20)	Re-used syringe (vs none/new)	0.65 (0.51, 0.82)
5-10 injections (vs 0)	1.64 (1.23, 2.20)	Family history of hepatitis (vs not)	2.57 (1.87, 3.53)
>10 injections (vs 0)	2.37 (1.68, 3.33)	Haemodialysis (vs never)	4.44 (1.63, 12.1)
Re-used syringe (vs none/new)	0.54 (0.44, 0.67)	Blood transfusion (vs never)	2.45 (1.53, 3.93)
Unknown syringe type (vs none/new)	0.42 (0.29, 0.62)		
Family history of hepatitis (vs not)	1.90 (1.38, 2.63)		

* Defined here as a p-value<0.05.

Table 4.2: Prevalence of risk factors/exposures and HCV infection, unadjusted and mutually adjusted ORs of HCV infection by age and sex.

Table 4.2a: Males and females aged 0-19 years.

	Males Aged 0-19					Females aged 0-19				
		HCV	OR (95% CI)		p-		HCV	OR (95% CI)		p-
Risk factor	**N (%)**	**N (%)**	**Unadjusted**	**Adjusted**	**value**	**N (%)**	**N (%)**	**Unadjusted**	**Adjusted**	**value**
Marital status (v. never)	11518 (98.7)	220 (1.9)	1	1		10415 (96.3)	219 (2.1)	1	1	
Married	129 (1.1)	4 (3.1)	1.64 (0.60, 4.51)	1.15 (0.44, 3.01)	0.771	392 (3.6)	12 (3.1)	1.47 (0.82, 2.65)	1.12 (0.61, 2.03)	0.722
other	22 (0.2)	1 (4.6)	2.45 (0.32, 18.4)	2.15 (0.26, 18.0)	0.478	14 (0.1)	0 (0.0)	NA	NA	
Urban (v. rural)	4463 (38.3)	80 (1.8)	0.89 (0.66, 1.19)	0.91 (0.67, 1.25)	0.574	4360 (40.4)	79 (1.8)	0.77 (0.55, 1.06)	0.84 (0.58, 1.22)	0.363
IDU (v. never)	10 (0.1)	1 (10.0)	5.67 (0.72, 45.0)	6.73 (0.84, 53.7)	0.072	11 (0.1)	1 (9.1)	4.60 (0.58, 36.2)	4.02 (0.37, 44.0)	0.254
Community risk										
Barber	587 (5.2)	24 (3.9)	2.21 (1.44, 3.40)	1.74 (1.09, 2.78)	0.020	22 (0.2)	0 (0.0)	NA	NA	
Sharing smoking eqpt.	49 (0.4)	1 (2.0)	1.06 (0.15, 7.73)	0.62 (0.09, 4.17)	0.621	15 (0.1)	0 (0.0)	NA	NA	
Sharing a toothbrush	86 (0.7)	2 (2.3)	1.21 (0.30, 4.90)	1.21 (0.31, 4.75)	0.780	75 (0.7)	2 (2.7)	1.26 (0.30, 5.30)	1.16 (0.27, 4.97)	0.844
Tattoo or acupuncture	24 (0.2)	0 (0.0)	NA	NA		11 (0.1)	3 (27.3)	17.4 (4.38, 69.2)	13.8 (3.67, 51.5)	<0.001
Ear or nose piercing	268 (2.3)	13 (4.9)	2.69 (1.47, 4.91)	2.71 (1.47, 4.99)	0.001	6151 (56.6)	155 (2.5)	1.56 (1.17, 2.08)	1.59 (1.19, 2.13)	0.002
Matam	23 (0.2)	1 (4.3)	2.32 (0.37, 14.7)	1.38 (0.19, 10.1)	0.748	8 (0.1)	0 (0.0)	NA	NA	
Socio-economic status										
Illiterate	3809 (32.6)	78 (2.1)	1.10 (0.83, 1.46)	1.03 (0.76, 1.39)	0.850	4406 (40.5)	122 (2.8)	1.65 (1.24, 2.20)	1.62 (1.19, 2.21)	0.002
Labourer	575 (4.9)	25 (4.4)	2.48 (1.61, 3.80)	1.99 (1.24, 3.21)	0.005	175 (1.6)	2 (1.1)	0.53 (0.13, 2.10)	0.42 (0.11, 1.70)	0.225
Healthcare risk										
No. of injections (v. 0)	3447 (29.6)	61 (1.8)	1	1		2996 (27.7)	59 (2.0)		1	
1-4 injections	5934 (50.9)	108 (1.8)	1.03 (0.73, 1.44)	0.88 (0.62, 1.26)	0.481	5617 (51.8)	130 (2.3)	1.18 (0.84, 1.65)	0.91 (0.65, 1.29)	0.601
5-10 injections	1905 (16.2)	48 (2.5)	1.43 (0.95, 2.16)	1.02 (0.65, 1.61)	0.933	1838 (17.0)	37 (2.0)	1.02 (0.67, 1.55)	0.68 (0.44, 1.07)	0.098
>10 injections	383 (3.3)	8 (2.1)	1.18 (0.56, 2.50)	0.89 (0.41, 1.94)	0.771	370 (3.4)	5 (1.4)	0.68 (0.27, 1.70)	0.51 (0.20, 1.30)	0.160
Syringe use (v. none/new)	9826 (84.2)	173 (1.8)	1	1		9118 (84.4)	176 (1.9)	1	1	
Re-used syringe	1201 (10.3)	37 (3.1)	1.77 (1.22, 2.59)	1.52 (1.00, 2.31)	0.048	1096 (10.0)	37 (3.4)	1.74 (1.13, 2.67)	1.78 (1.19, 2.67)	0.005
Unknown syringe type	642 (5.5)	15 (2.3)	1.33 (0.76, 2.36)	1.30 (0.71, 2.36)	0.392	607 (5.6)	18 (3.0)	1.52 (0.64, 3.60)	1.48 (0.62, 3.53)	0.374
Dentist	31 (0.3)	0 (0.0)	NA	NA		44 (0.4)	2 (4.6)	2.19 (0.52, 9.22)	2.54 (0.59, 10.8)	0.209
Family history hepatitis	205 (1.8)	10 (4.9)	2.68 (1.36, 5.29)	2.63 (1.34, 5.16)	0.005	213 (2.0)	4 (1.9)	0.88 (0.32, 2.36)	0.94 (0.34, 2.58)	0.905
Haemodialysis	10 (0.1)	0 (0.0)	NA	NA		13 (0.1)	0 (0.0)	NA	NA	
Blood transfusion	16 (0.1)	0 (0.0)	NA	NA		19 (0.2)	2 (10.5)	5.43 (1.24, 23.73)	11.0 (0.89, 137)	0.061
History of surgery	132 (1.1)	1 (0.8)	0.38 (0.05, 2.73)	0.41 (0.06, 3.05)	0.386	104 (1.0)	3 (2.9)	1.37 (0.43, 4.33)	0.55 (0.07, 4.21)	0.566
TOTAL	**11669 (100)**	**225 (1.9)**				**10821 (100)**	**213 (2.0)**			

IDU: injecting drug use; NA: not applicable – no cases of HCV infection

Table 4.2b: Males and females aged 20-29 years.

	Males Aged 20-29					Females aged 20-29				
		HCV	OR (95% CI)		p-		HCV	OR (95% CI)		p-
Risk factor	**N (%)**	**N (%)**	**Unadjusted**	**Adjusted**	**value**	**N (%)**	**N (%)**	**Unadjusted**	**Adjusted**	**value**
Marital status (v. never)	3121 (70.6)	108 (3.5)	1	1		1870 (43.7)	63 (3.4)	1	1	
Married	1284 (29.1)	64 (5.0)	1.45 (1.05, 1.99)	1.32 (0.95, 1.84)	0.097	2373 (55.5)	138 (5.8)	1.77 (1.31,2.40)	1.58 (1.15, 2.19)	0.005
Other	15 (0.3)	0 (0.0)	NA	NA		29 (0.7)	3 (10.3)	3.31 (0.98,11.2)	3.76 (1.07, 13.3)	0.039
Urban (v. rural)	1897 (42.9)	69 (3.6)	0.89 (0.64, 1.22)	0.89 (0.64, 1.24)	0.501	1799 (42.1)	77 (4.3)	0.83 (0.62,1.11)	0.84 (0.61, 1.17)	0.311
IDU (v. never)	7 (0.2)	0 (0.0)	NA	NA		6 (0.1)	0 (0.0)	NA	NA	
Community risk										
Barber	1823 (41.2)	90 (4.9)	1.59 (1.17, 2.17)	1.43 (1.01, 2.01)	0.042	26 (0.6)	3 (11.5)	2.62 (0.78,8.87)	4.22 (1.01, 17.6)	0.048
Sharing smoking eqpt.	217 (4.9)	12 (5.5)	1.48 (0.82, 2.67)	1.15 (0.61, 2.16)	0.661	37 (0.9)	4 (10.8)	2.44 (0.85,7.02)	1.45 (0.46, 4.55)	0.523
Sharing a toothbrush	72 (1.6)	5 (6.9)	1.87 (0.77, 4.51)	1.51 (0.59, 3.87)	0.388	29 (0.7)	2 (6.9)	1.48 (0.33,6.58)	1.61 (0.36, 7.11)	0.532
Tattoo or acupuncture	47 (1.1)	3 (6.4)	1.70 (0.53, 5.46)	1.14 (0.35, 3.74)	0.832	24 (0.6)	4 (16.7)	4.05 (1.35,12.2)	3.42 (1.05, 11.2)	0.042
Ear or nose piercing	111 (2.5)	8 (7.2)	1.94 (0.93, 4.07)	2.20 (0.99, 4.88)	0.053	3349 (78.4)	181 (5.4)	2.23 (1.44,3.46)	2.30 (1.40, 3.76)	0.001
Matam	14 (0.3)	1 (7.1)	1.91 (0.33, 11.0)	2.04 (0.39, 10.7)	0.402	6 (0.1)	0 (0.0)	NA	NA	
Socio-economic status										
Illiterate	1168 (26.5)	47 (4.0)	1.05 (0.74, 1.48)	0.93 (0.64, 1.34)	0.687	2129 (50.2)	111 (5.2)	1.21 (0.91,1.61)	0.98 (0.71, 1.37)	0.927
Labourer	817 (18.5)	51 (6.2)	1.92 (1.35, 2.72)	1.75 (1.18, 2.59)	0.005	88 (2.1)	5 (5.7)	1.21 (0.48,3.03)	1.15 (0.45, 2.91)	0.771
Healthcare risk										
No. of injections (v. 0)	1049 (23.7)	35 (3.3)	1	1		798 (18.7)	31 (3.9)	1	1	
1-4 injections	2032 (46.0)	80 (3.9)	1.19 (0.79, 1.79)	1.13 (0.64, 2.00)	0.671	2043 (47.8)	82 (4.0)	1.03 (0.67,1.60)	0.80 (0.44, 1.47)	0.477
5-10 injections	1090 (24.7)	42 (3.9)	1.16 (0.73, 1.86)	1.07 (0.57, 2.00)	0.841	1122 (26.3)	68 (6.1)	1.60 (1.02,2.49)	1.12 (0.58, 2.16)	0.729
>10 injections	249 (5.6)	15 (6.0)	1.86 (0.98, 3.53)	2.02 (0.92, 4.47)	0.081	309 (7.2)	23 (7.4)	1.99 (1.13,3.51)	1.44 (0.68, 3.05)	0.342
Syringe use (v. none/new)	1600 (36.2)	62 (3.9)	1	1		1341 (31.4)	57 (4.3)	1	1	
Re-used syringe	2559 (57.9)	103 (4.0)	1.22 (0.82, 1.81)	0.91 (0.57, 1.46)	0.710	2656 (62.2)	131 (4.9)	1.28 (0.85,1.94)	0.95 (0.59, 1.55)	0.844
Unknown syringe type	261 (5.9)	7 (2.7)	0.80 (0.32, 1.98)	0.55 (0.21, 1.40)	0.209	275 (6.4)	16 (5.8)	1.53 (0.80,2.92)	1.10 (0.53, 2.26)	0.805
Dentist	49 (1.1)	0 (0.0)	NA	NA		52 (1.2)	2 (3.9)	0.80 (0.19,3.30)	0.75 (0.17, 3.29)	0.701
Family history hepatitis	132 (3.0)	14 (10.6)	3.10 (1.63, 5.92)	2.83 (1.47, 5.43)	0.002	163 (3.8)	16 (9.8)	2.27 (1.30,3.97)	1.96 (1.09, 3.51)	0.024
Haemodialysis	6 (0.1)	1 (16.7)	4.96 (0.58, 42.7)	10.1 (1.19, 86.5)	0.034	6 (0.1)	1 (16.7)	4.00 (0.47,34.4)	2.34 (0.14, 38.7)	0.552
Blood transfusion	9 (0.2)	0 (0.0)	NA	NA		56 (1.3)	8 (14.4)	3.42 (1.60,7.31)	5.76 (1.73, 19.2)	0.004
History of surgery	151 (3.4)	2 (1.3)	0.32 (0.08, 1.32)	0.29 (0.06, 1.28)	0.103	185 (4.3)	11 (6.0)	1.28 (0.68,2.38)	0.45 (0.16, 1.27)	0.132
TOTAL	**4420 (100)**	**172 (3.9)**				**4272 (100)**	**204 (4.8)**			

IDU: injecting drug use; NA: not applicable – no cases of HCV infection

Table 4.2c: Males and females aged ≥30 years.

	Males aged ≥ 30 years					Females aged ≥ 30 years				
Risk factor	**N (%)**	**HCV N (%)**	**OR (95% CI) Unadjusted**	**Adjusted**	**p-value**	**N (%)**	**HCV N (%)**	**OR (95% CI) Unadjusted**	**Adjusted**	**p-value**
Marital status (v. never)	654 (7.9)	39 (6.0)	1	1		422 (5.6)	23 (5.5)			
Married	7310 (88.8)	739 (10.1)	1.77 (1.28, 2.44)	1.61 (1.16, 2.22)	0.004	6317 (85.1)	569 (9.0)	1.70 (1.11, 2.61)	1.51 (0.98, 2.34)	0.061
Other	272 (3.3)	27 (9.9)	1.73 (1.05, 2.85)	1.44 (0.86, 2.40)	0.167	686 (9.3)	61 (8.9)	1.68 (1.02, 2.76)	1.42 (0.85, 2.36)	0.183
Urban (v. rural)	3257 (39.6)	330 (10.1)	1.07 (0.92, 1.24)	1.17 (0.99, 1.37)	0.061	3039 (41.1)	255 (8.4)	0.92 (0.77, 1.09)	0.96 (0.79, 1.15)	0.636
IDU (v. never)	12 (0.2)	3 (25.0)	3.08 (0.83, 11.4)	1.89 (0.42, 8.45)	0.404	11 (0.2)	3 (27.3)	3.90 (1.17, 13.0)	2.38 (0.74, 7.70)	0.147
Community risk										
Barber	3580 (43.5)	441 (12.3)	1.66 (1.43, 1.92)	1.45 (1.24, 1.70)	<0.001	49 (0.7)	4 (8.2)	0.92 (0.33, 2.57)	0.97 (0.33, 2.78)	0.948
Sharing smoking eqpt.	991 (12.0)	132 (13.3)	1.50 (1.23, 1.83)	1.23 (0.99, 1.53)	0.064	126 (1.7)	10 (7.9)	0.89 (0.46, 1.72)	0.70 (0.36, 1.37)	0.398
Sharing a toothbrush	161 (2.0)	22 (13.6)	1.46 (0.93, 2.29)	1.27 (0.78, 2.06)	0.335	62 (0.8)	8 (12.9)	1.55 (0.74, 3.22)	1.47 (0.68, 3.20)	0.330
Tattoo or acupuncture	78 (1.0)	8 (10.3)	1.06 (0.51, 2.20)	0.88 (0.40, 1.89)	0.735	46 (0.6)	1 (2.2)	0.23 (0.03, 1.68)	0.20 (0.03, 1.53)	0.121
Ear or nose piercing	159 (1.9)	14 (8.8)	0.89 (0.51, 1.54)	1.01 (0.58, 1.77)	0.968	6098 (82.1)	563 (9.2)	1.39 (1.09, 1.77)	1.27 (0.98, 1.66)	0.070
Matam	36 (0.4)	2 (5.6)	0.54 (0.13, 2.30)	0.42 (0.10, 1.81)	0.243	10 (0.1)	2 (20.0)	2.60 (0.53, 12.7)	2.62 (0.49, 14.1)	0.263
Socio-economic status										
Illiterate	3765 (45.7)	410 (10.9)	1.26 (1.09, 1.46)	1.30 (1.11, 1.52)	0.001	5494 (74.0)	518 (9.4)	1.38 (1.13, 1.69)	1.43 (1.15, 1.78)	0.001
Labourer	1736 (21.1)	232 (13.4)	1.59 (1.35, 1.88)	1.41 (1.18, 1.67)	<0.001	145 (2.0)	25 (17.2)	2.20 (1.43, 3.41)	2.05 (1.30, 3.23)	0.002
Healthcare risk										
No. of injections (v. 0)	1536 (18.7)	130 (8.5)	1	1		1081 (14.6)	83 (7.8)	1	1	
1-4 injections	3649 (44.3)	362 (9.9)	1.19 (0.97, 1.47)	1.69 (1.29, 2.20)	<0.001	3275 (44.1)	244 (7.5)	0.95 (0.73, 1.24)	1.23 (0.89, 1.70)	0.218
5-10 injections	2280 (27.7)	221 (9.7)	1.16 (0.93, 1.46)	1.64 (1.23, 2.20)	0.001	2222 (30.0)	224 (10.1)	1.33 (1.02, 1.73)	1.65 (1.17, 2.33)	0.004
>10 injections	771 (9.4)	92 (11.9)	1.47 (1.10, 1.95)	2.37 (1.68, 3.33)	<0.001	847 (11.4)	101 (11.9)	1.60 (1.18, 2.19)	1.92 (1.32, 2.79)	0.001
Syringe use (v. none/new)	2532 (30.7)	290 (11.5)	1	1		2002 (27.0)	191 (9.6)	1	1	
	51784	475 (9.2)				4937 (66.5)	415 (8.4)			
Re-used syringe	(62.9)		1.09 (0.89, 1.34)	0.54 (0.44, 0.67)	<0.001			1.09 (0.85, 1.40)	0.65 (0.51, 0.82)	<0.001
Unknown syringe type	520 (6.3)	40 (7.7)	0.90 (0.62, 1.30)	0.42 (0.29, 0.62)	<0.001	486 (6.6)	46 (9.5)	1.24 (0.85, 1.81)	0.76 (0.52, 1.12)	0.164
Dentist	245 (3.0)	30 (12.2)	1.30 (0.88, 1.92)	1.14 (0.77, 1.70)	0.520	270 (3.6)	29 (10.7)	1.26 (0.85, 1.87)	1.08 (0.73, 1.60)	0.695
Family history hepatitis	296 (3.6)	53 (17.9)	2.08 (1.53, 2.84)	1.90 (1.38, 2.63)	<0.001	280 (3.8)	60 (21.4)	3.01 (2.22, 4.08)	2.57 (1.87, 3.53)	<0.001
Haemodialysis	13 (0.2)	2 (15.4)	1.68 (0.37, 7.59)	1.67 (0.38, 7.34)	0.499	18 (0.2)	6 (33.3)	5.22 (1.95, 13.9)	4.44 (1.63, 12.1)	0.004
Blood transfusion	77 (0.9)	12 (15.6)	1.71 (0.92, 3.19)	1.95 (0.95, 4.01)	0.068	222 (3.0)	47 (21.2)	2.92 (2.09, 4.08)	2.45 (1.53, 3.93)	<0.001
History of surgery	594 (7.2)	56 (9.4)	0.96 (0.72, 1.27)	0.83 (0.60, 1.16)	0.276	673 (9.1)	86 (13.2)	1.60 (1.25, 2.03)	0.99 (0.70, 1.39)	0.942
TOTAL	**8236 (100)**	**805 (9.8)**				**7425 (100)**	**653 (8.8)**			

IDU: injecting drug use; NA: not applicable – no cases of HCV infection

4.3.3. Association of grouped exposures and risk factors with HCV

The HCV prevalence and the unadjusted and adjusted ORs (95% CI) of HCV infection for the community, healthcare, and socio-economic status grouped exposures are shown in table 4.3, separately for males and females. Community, healthcare, and socio-economic status exposures were all strongly associated with HCV infection. The increase in adjusted odds of prevalent HCV infection associated with one community exposure (versus none), aOR for males 1.22 (95% CI: 1.06, 1.41) and for females 1.46 (95% CI: 1.21, 1.76), was similar to that associated with one healthcare exposure (versus none), aOR for males 1.21 (95% CI: 1.06, 1.39) and for females 1.40 (95% CI: 1.22, 1.61). Although the association of HCV infection with multiple healthcare exposures (versus none) [aOR for males 3.31 (95% CI: 1.69, 6.47) and females 4.17 (95% CI: 2.84, 6.14)] was much stronger than that for multiple community factors (versus none) [aOR for males 1.34 (95% CI: 1.06, 1.69) and for females 2.07 (95% CI: 1.25, 3.44)], only a small proportion of the population was exposed to multiple healthcare exposures (females 0.8%; males 0.2%). Older age was associated with HCV infection, with a more than doubling of the odds among males aged ≥40 years compared with those aged 20-29 years, aORs 2.43 (95% CI: 1.90, 3.09), 2.41 (95% CI: 1.85, 3.14), and 2.22 (95% CI: 1.71, 2.88), for those aged 40-49, 50-59, and ≥60, respectively. Ever being married (versus never) was also associated with HCV infection, aOR for males 1.43 (95% CI: 1.14, 1.78) and for females 1.54 (95% CI: 1.23, 1.94). Results from the sensitivity analyses – both those excluding provinces with very low prevalence (table 4.4) and those not adjusting for province (table 4.5) – were similar to the main analysis, which included all provinces and adjusted for province.

A separate analysis where I did not group the exposures that comprised the community, healthcare, and socio-economic status variables (table 4.6) showed that a high percentage of those who had had haemodialysis (10% and 19% for men and women, respectively) or a blood transfusion (12% and 19% for men and women) had HCV infection. However, few individuals had undergone these procedures – less than 500 altogether. There was also a high prevalence of HCV in men that had shared smoking equipment, 12%.

Table 4.3: Prevalence of risk factors/exposures and HCV infection, unadjusted and mutually adjusted ORs of HCV infection by sex.

Risk Factor	OR (95% CI) for HCV infection					OR (95% CI) for HCV infection				
	Males					Females				
	Freq.	HCV Prev.	Unadjusted	Adjusted	Adj. p-value	Freq.	HCV Prev.	Unadjusted	Adjusted	Adj. p-value
Never married	15,293	2%	1	1		12,707	2%	1	1	
Ever married	9,032	9%	4.14 (3.65, 4.70)	1.43 (1.14, 1.78)	p=0.002	9,811	8%	3.53 (3.07, 4.06)	1.54 (1.23, 1.94)	p<0.001
Community risks 0	17,306	3%	1	1		6,796	3%	1	1	
Community risks 1	6,105	9%	2.73 (2.41, 3.10)	1.22 (1.06, 1.41)	p=0.006	15,492	6%	2.18 (1.85, 2.58)	1.46 (1.21, 1.76)	p<0.001
Community risks ≥2	914	12%	4.10 (3.30, 5.10)	1.34 (1.06, 1.69)	p=0.013	230	10%	3.82 (2.41, 6.07)	2.07 (1.25, 3.44)	p=0.005
S-ES risks 0	14,166	4%	1	1		10,389	3%	1	1	
S-ES risks ≥1	10,159	7%	1.84 (1.64, 2.07)	1.33 (1.17, 1.51)	p<0.001	12,129	6%	2.00 (1.75, 2.30)	1.55 (1.33, 1.81)	p<0.001
Healthcare risks 0	17,570	4%	1	1		15,660	4%	1	1	
Healthcare risks 1	6,701	6%	1.45 (1.28, 1.65)	1.21 (1.06, 1.39)	p=0.005	6,675	7%	1.75 (1.54, 1.99)	1.40 (1.22, 1.61)	p<0.001
Healthcare risks ≥2	54	20%	5.57 (2.86, 10.83)	3.31 (1.69, 6.47)	p<0.001	183	22%	7.16 (5.00, 10.26)	4.17 (2.84, 6.14)	p<0.001
Punjab (Province)	13,186	7%	1	1		11,926	7%	1	1	
Sindh	4,640	5%	0.73 (0.63, 0.86)	0.69 (0.59, 0.82)	p<0.001	4,221	5%	0.75 (0.64, 0.89)	0.67 (0.56, 0.79)	p<0.001
Baluchistan	3,831	1%	0.15 (0.11, 0.22)	0.16 (0.11, 0.22)	p<0.001	3,766	1%	0.16 (0.11, 0.22)	0.14 (0.10, 0.19)	p<0.001
North West Frontier	2,668	1%	0.18 (0.13, 0.27)	0.19 (0.13, 0.28)	p<0.001	2,605	2%	0.24 (0.17, 0.33)	0.20 (0.14, 0.29)	p<0.001
Age 0-9	5,309	2%	0.36 (0.27, 0.49)	0.48 (0.35, 0.66)	p<0.001	5,013	2%	0.39 (0.30, 0.50)	0.63 (0.46, 0.85)	p=0.003
Age 10-19	6,360	2%	0.59 (0.47, 0.74)	0.77 (0.60, 0.99)	p=0.041	5,808	2%	0.48 (0.38, 0.60)	0.69 (0.53, 0.89)	p=0.005
Age 20-29	4,420	4%	1	1		4,272	5%	1	1	
Age 30-39	2,831	7%	1.90 (1.54, 2.34)	1.53 (1.20, 1.95)	p<0.001	2,910	8%	1.84 (1.52, 2.23)	1.47 (1.20, 1.81)	p<0.001
Age 40-49	2,292	11%	3.17 (2.60, 3.88)	2.43 (1.90, 3.09)	p<0.001	2,109	9%	1.88 (1.54, 2.31)	1.40 (1.12, 1.75)	p=0.003
Age 50-59	1,479	11%	3.04 (2.43, 3.80)	2.41 (1.85, 3.14)	p<0.001	1,289	10%	2.20 (1.75, 2.76)	1.55 (1.21, 1.98)	p<0.001
Age ≥60	1,634	11%	3.06 (2.47, 3.79)	2.22 (1.71, 2.88)	p<0.001	1,117	9%	1.90 (1.48, 2.43)	1.25 (0.96, 1.63)	p=0.100

S-ES: socio-economic status

Table 4.4: Prevalence of risk factors/exposures and HCV infection, unadjusted and mutually adjusted ORs of HCV infection by sex, with the Baluchistan and North-West Frontier provinces omitted.

Risk Factor	OR (95% CI) for HCV infection					OR (95% CI) for HCV infection				
	Males					Females				
	Freq.	HCV Prev.	Unadjusted	Adjusted	Adj. p-value	Freq.	HCV Prev.	Unadjusted	Adjusted	Adj. p-value
Never married	11,175	3%	1	1		9,267	3%	1	1	
Ever married	6,651	12%	4.22 (3.70, 4.82)	1.47 (1.17, 1.86)	p=0.001	6,880	10%	3.67 (3.17, 4.25)	1.57 (1.23, 2.01)	p<0.001
Community risks 0	11,858	4%	1	1		5,076	3%	1	1	
Community risks 1	5,138	10%	2.45 (2.15, 2.80)	1.27 (1.10, 1.48)	p=0.002	10,948	7%	2.25 (1.90, 2.67)	1.44 (1.18, 1.75)	p<0.001
Community risks ≥2	830	13%	3.50 (2.80, 4.37)	1.43 (1.13, 1.81)	p=0.003	123	15%	5.15 (3.07, 8.63)	2.22 (1.27, 3.87)	p=0.005
S-ES risks 0	10,206	5%	1	1		8,002	4%	1	1	
S-ES risks ≥1	7,620	8%	1.74 (1.54, 1.97)	1.28 (1.12, 1.46)	p<0.001	8,145	8%	2.21 (1.91, 2.55)	1.52 (1.30, 1.78)	p<0.001
Healthcare risks 0	13,165	6%	1	1		11,409	5%	1	1	
Healthcare risks 1	4,619	8%	1.50 (1.31, 1.72)	1.18 (1.02, 1.36)	p=0.024	4,584	9%	1.82 (1.58, 2.09)	1.39 (1.21, 1.61)	p<0.001
Healthcare risks ≥2	42	26%	5.99 (3.00, 11.96)	3.54 (1.76, 7.14)	p<0.001	154	25%	6.27 (4.28, 9.17)	4.05 (2.71, 6.07)	p<0.001
Punjab (Province)	13,186	7%	1	1		11,926	7%	1	1	
Sindh	4,640	5%	0.73 (0.63, 0.86)	0.70 (0.59, 0.82)	p<0.001	4,221	5%	0.75 (0.64, 0.89)	0.67 (0.56, 0.79)	p<0.001
Age 0-9	3,737	2%	0.40 (0.30, 0.54)	0.53 (0.38, 0.72)	p<0.001	3,587	3%	0.41 (0.32, 0.54)	0.67 (0.49, 0.92)	p=0.012
Age 10-19	4,641	3%	0.61 (0.48, 0.77)	0.79 (0.61, 1.02)	p=0.076	4,175	3%	0.48 (0.38, 0.61)	0.70 (0.53, 0.92)	p=0.010
Age 20-29	3,350	5%	1	1		3,079	6%	1	1	
Age 30-39	2,121	9%	1.98 (1.59, 2.47)	1.55 (1.21, 2.00)	p<0.001	2,055	11%	1.89 (1.54, 2.31)	1.46 (1.17, 1.81)	p=0.001
Age 40-49	1,706	14%	3.38 (2.74, 4.16)	2.45 (1.90, 3.15)	p<0.001	1,477	12%	2.03 (1.64, 2.52)	1.45 (1.15, 1.83)	p=0.002
Age 50-59	1,058	15%	3.40 (2.69, 4.29)	2.48 (1.88, 3.26)	p<0.001	925	13%	2.24 (1.76, 2.86)	1.54 (1.19, 1.99)	p=0.001
Age ≥60	1,213	13%	3.03 (2.42, 3.80)	2.09 (1.59, 2.75)	p<0.001	849	11%	1.95 (1.50, 2.52)	1.31 (1.00, 1.73)	p=0.053

S-ES: socio-economic status

Table 4.5: Prevalence of risk factors/exposures and HCV infection, unadjusted and mutually adjusted ORs of HCV infection by sex, without adjustment for province.

Risk Factor	OR (95% CI) for HCV infection					OR (95% CI) for HCV infection				
	Males					Females				
	Freq.	HCV Prev.	Unadjusted	Adjusted	Adj. p-value	Freq.	HCV Prev.	Unadjusted	Adjusted	Adj. p-value
Never married	15,293	2%	1	1		12,707	2%	1	1	
Ever married	9,032	9%	4.14 (3.65, 4.70)	1.34 (1.07, 1.67)	p=0.010	9,811	8%	3.53 (3.07, 4.06)	1.46 (1.17, 1.83)	p<0.001
Community risks 0	17,306	3%	1	1		6,796	3%	1	1	
Community risks 1	6,105	9%	2.73 (2.41, 3.10)	1.63 (1.42, 1.87)	p<0.001	15,492	6%	2.18 (1.85, 2.58)	1.45 (1.21, 1.73)	p<0.001
Community risks ≥2	914	12%	4.10 (3.30, 5.10)	1.89 (1.50, 2.38)	p<0.001	230	10%	3.82 (2.41, 6.07)	1.62 (0.99, 2.63)	p=0.052
S-ES risks 0	14,166	4%	1	1		10,389	3%	1	1	
S-ES risks ≥1	10,159	7%	1.84 (1.64, 2.07)	1.35 (1.19, 1.53)	p<0.001	12,129	6%	2.00 (1.75, 2.30)	1.35 (1.16, 1.57)	p<0.001
Healthcare risks 0	17,570	4%	1	1		15,660	4%	1	1	
Healthcare risks 1	6,701	6%	1.45 (1.28, 1.65)	1.02 (0.89, 1.17)	p=0.747	6,675	7%	1.75 (1.54, 1.99)	1.26 (1.10, 1.44)	p<0.001
Healthcare risks ≥2	54	20%	5.57 (2.86, 10.83)	2.69 (1.37, 5.28)	p=0.004	183	22%	7.16 (5.00, 10.26)	3.96 (2.72, 5.76)	p<0.001
Age 0-9	5,309	2%	0.36 (0.27, 0.49)	0.50 (0.37, 0.69)	p<0.001	5,013	2%	0.39 (0.30, 0.50)	0.60 (0.45, 0.82)	p<0.001
Age 10-19	6,360	2%	0.59 (0.47, 0.74)	0.80 (0.63, 1.03)	p=0.087	5,808	2%	0.48 (0.38, 0.60)	0.65 (0.51, 0.85)	p<0.001
Age 20-29	4,420	4%	1	1		4,272	5%	1	1	
Age 30-39	2,831	7%	1.90 (1.54, 2.34)	1.54 (1.21, 1.95)	p<0.001	2,910	8%	1.84 (1.52, 2.23)	1.51 (1.23, 1.85)	p<0.001
Age 40-49	2,292	11%	3.17 (2.60, 3.88)	2.41 (1.90, 3.07)	p<0.001	2,109	9%	1.88 (1.54, 2.31)	1.46 (1.17, 1.81)	p<0.001
Age 50-59	1,479	11%	3.04 (2.43, 3.80)	2.35 (1.81, 3.06)	p<0.001	1,289	10%	2.20 (1.75, 2.76)	1.66 (1.31, 2.11)	p<0.001
Age ≥60	1,634	11%	3.06 (2.47, 3.79)	2.28 (1.76, 2.95)	p<0.001	1,117	9%	1.90 (1.48, 2.43)	1.44 (1.11, 1.87)	p=0.006

S-ES: socio-economic status

Table 4.6: Prevalence of individual risk factors/exposures and HCV infection, unadjusted and mutually adjusted ORs of HCV infection by sex.

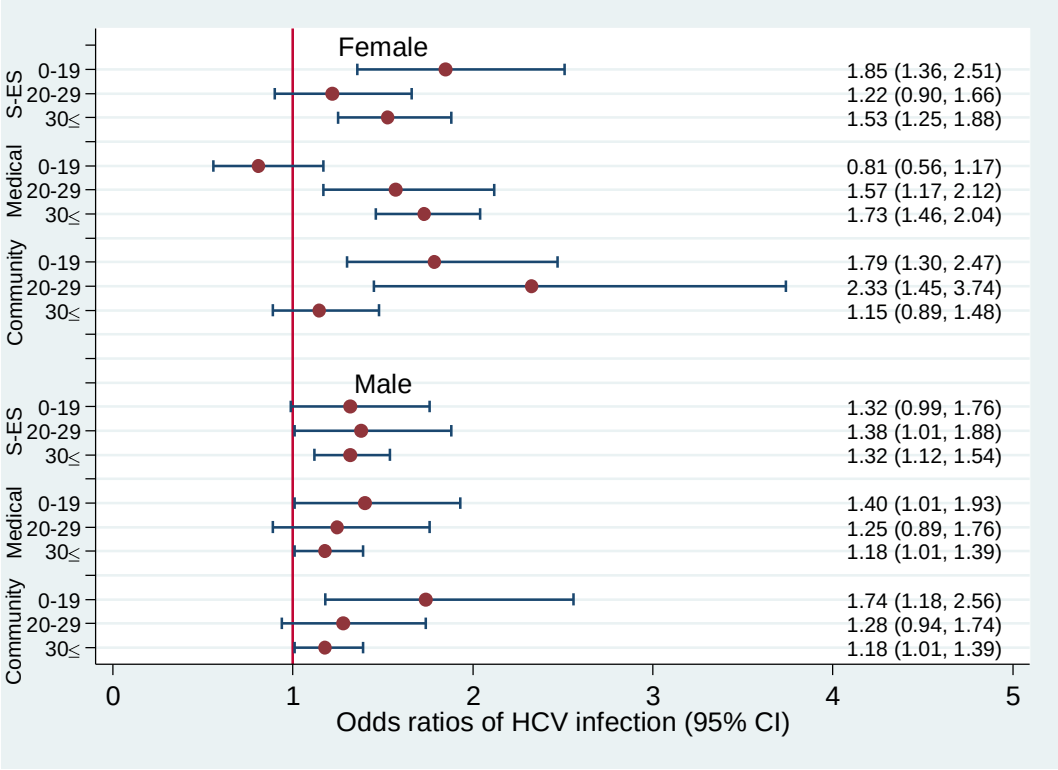
Risk Factor	OR (95% CI) for HCV infection					OR (95% CI) for HCV infection				
	Males					Females				
	Freq.	HCV Prev.	Unadjusted	Adjusted	Adj. p-value	Freq.	HCV Prev.	Unadjusted	Adjusted	Adj. p-value
Never married	15,293	2%	1	1		12,707	2%	1	1	
Ever married	9,032	9%	4.14 (3.65, 4.70)	1.42 (1.14, 1.78)	p=0.002	9,811	8%	3.53 (3.07, 4.06)	1.52 (1.21, 1.92)	p<0.001
Barber	6,014	9%	2.78 (2.46, 3.13)	1.18 (1.03, 1.35)	p=0.020	97	7%	1.54 (0.71, 3.33)	1.46 (0.66, 3.24)	p=0.356
Ear or nose piercing	539	6%	1.35 (0.93, 1.95)	1.58 (1.07, 2.33)	p=0.022	15,603	6%	2.18 (1.85, 2.56)	1.49 (1.23, 1.79)	p<0.001
Tattoo/acupuncture	149	7%	1.54 (0.83, 2.85)	1.04 (0.56, 1.94)	p=0.900	81	10%	2.17 (1.07, 4.38)	2.42 (1.12, 5.25)	p=0.025
Sharing smoking eqpt.	1,257	12%	2.72 (2.26, 3.27)	1.13 (0.93, 1.38)	p=0.218	178	8%	1.69 (0.97, 2.95)	1.00 (0.57, 1.75)	p=0.991
Illiterate	8,744	6%	1.46 (1.29, 1.64)	1.15 (1.01, 1.31)	p=0.038	12,029	6%	2.01 (1.75, 2.30)	1.57 (1.35, 1.83)	p<0.001
Labourer	3,128	10%	2.48 (2.16, 2.85)	1.25 (1.07, 1.46)	p=0.004	408	8%	1.70 (1.19, 2.42)	1.30 (0.90, 1.88)	p=0.161
≥5 Medical Injections	6,678	6%	1.48 (1.30, 1.68)	1.24 (1.08, 1.42)	p=0.002	6,708	7%	1.77 (1.55, 2.01)	1.37 (1.19, 1.57)	p<0.001
Haemodialysis	29	10%	2.22 (0.67, 7.36)	2.01 (0.59, 6.80)	p=0.261	37	19%	4.62 (2.06, 10.4)	3.20 (1.38, 7.39)	p=0.007
Blood transfusion	102	12%	2.58 (1.41, 4.73)	1.52 (0.82, 2.82)	p=0.181	297	19%	4.88 (3.61, 6.60)	2.90 (2.10, 4.00)	p<0.001
Punjab (Province)	13,186	7%	1	1		11,926	7%	1	1	
Sindh	4,640	5%	0.73 (0.63, 0.86)	0.69 (0.58, 0.81)	p<0.001	4,221	5%	0.75 (0.64, 0.89)	0.65 (0.55, 0.77)	p<0.001
Baluchistan	3,831	1%	0.15 (0.11, 0.22)	0.16 (0.11, 0.23)	p<0.001	3,766	1%	0.16 (0.11, 0.22)	0.14 (0.10, 0.19)	p<0.001
North West Frontier	2,668	1%	0.18 (0.13, 0.27)	0.20 (0.14, 0.28)	p<0.001	2,605	2%	0.24 (0.17, 0.33)	0.20 (0.14, 0.28)	p<0.001
Age 0-9	5,309	2%	0.36 (0.27, 0.49)	0.49 (0.36, 0.67)	p<0.001	5,013	2%	0.39 (0.30, 0.50)	0.63 (0.46, 0.85)	p=0.003
Age 10-19	6,360	2%	0.59 (0.47, 0.74)	0.76 (0.59, 0.97)	p=0.028	5,808	2%	0.48 (0.38, 0.60)	0.69 (0.53, 0.89)	p=0.004
Age 20-29	4,420	4%	1	1		4,272	5%	1	1	
Age 30-39	2,831	7%	1.90 (1.54, 2.34)	1.55 (1.22, 1.97)	p<0.001	2,910	8%	1.84 (1.52, 2.23)	1.47 (1.19, 1.81)	p=0.003
Age 40-49	2,292	11%	3.17 (2.60, 3.88)	2.45 (1.92, 3.12)	p<0.001	2,109	9%	1.88 (1.54, 2.31)	1.39 (1.11, 1.74)	p=0.004
Age 50-59	1,479	11%	3.04 (2.43, 3.80)	2.45 (1.88, 3.18)	p<0.001	1,289	10%	2.20 (1.75, 2.76)	1.55 (1.21, 1.98)	p<0.001
Age ≥60	1,634	11%	3.06 (2.47, 3.79)	2.29 (1.76, 2.98)	p<0.001	1,117	9%	1.90 (1.48, 2.43)	1.25 (0.96, 1.63)	p=0.101

Eqpt: equipment

4.3.4. Differences by age in associations of grouped risk factors with HCV

I repeated the analyses examining the grouped risk factors seen in table 4.3, stratifying by age as well as sex (figure 4.2) and presenting the risk factors as binary variables (any exposure versus none). Low socio-economic status and having community risks were associated with an increased odds of HCV for females aged 0-19, whilst having medical and community risks were associated for women aged 20-29, and low socio-economic status and having medical risks were associated with increased odds of HCV for women aged ≥30. For men aged 0-19, having medical and community risks were associated with increased odds of HCV, whilst for those aged 20-29 HCV was positively associated with low socio-economic status. For men aged ≥30 all of the risk domains were associated with prevalent HCV.

Figure 4.2: Trends in adjusted odds ratio of HCV infection by age for community, medical, and S-ES risk (presence versus absence), stratified by sex.

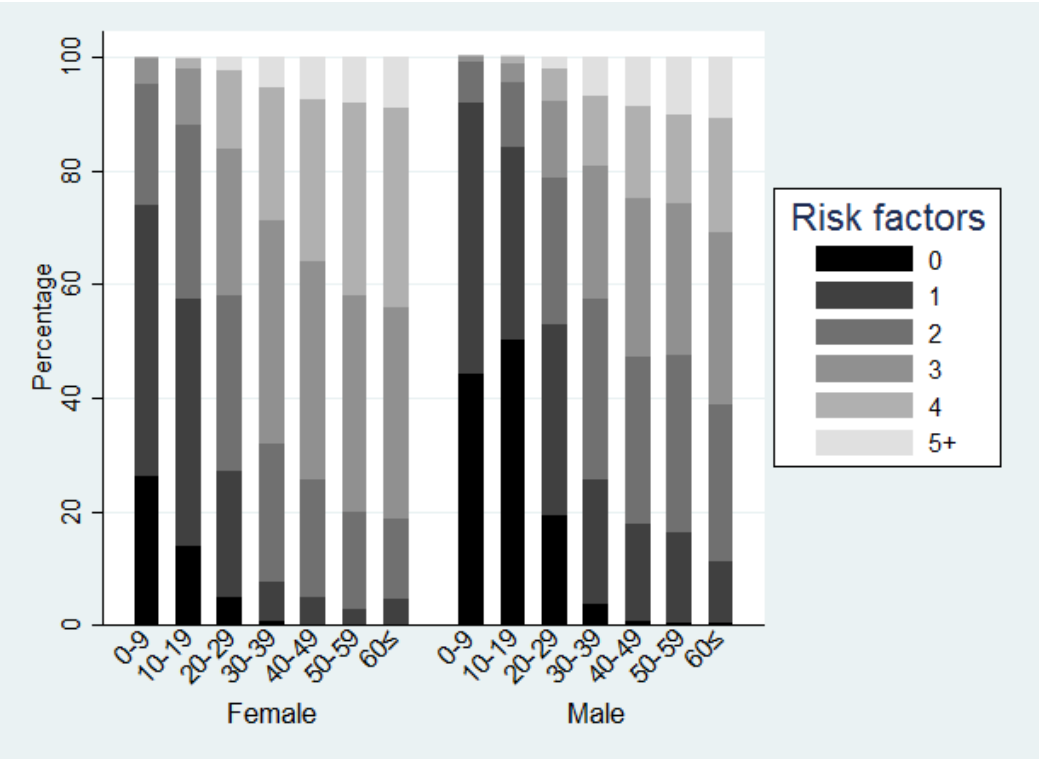


S-ES: socio-economic status

4.3.5. Association of cumulative number of risk factors/exposures with HCV

The cumulative number of exposures increased with age, among both females and males (figure 4.3). The prevalence of HCV infection also increased as the number of exposures increased (figure 4.4). The HCV prevalence for individuals with 0, 1, 2, 3, 4, and ≥5 lifetime exposures was 2%, 3%, 5%, 8%, 11%, and 15%, respectively, with the majority of HCV infections (77%) being among individuals with two or more risk factor exposures. Figure 4.5 plots HCV prevalence by number of risk factors, for males and females. A clear association between more risk factors and increasing HCV prevalence is shown, with similar prevalence for both sexes. The aOR of HCV per additional exposure was 1.51 (95% CI: 1.41, 1.61) for females and 1.21 (95% CI: 1.15, 1.27) for males. In Punjab and Sindh, the prevalences for individuals with ≥5 exposures were 13% and 17%, respectively.

Figure 4.3: Proportion of the population experiencing different numbers of exposures* for HCV infection by age and sex.



* Exposures included in this analysis were having ≥5 injections, haemodialysis, blood transfusions, going to the barber, ear/nose piercing, tattoo/acupuncture, sharing smoking equipment, marriage, illiteracy, and being a labourer.

Figure 4.4: Percentage of population, HCV prevalence, and percentage of infections among individuals with different numbers of exposures.

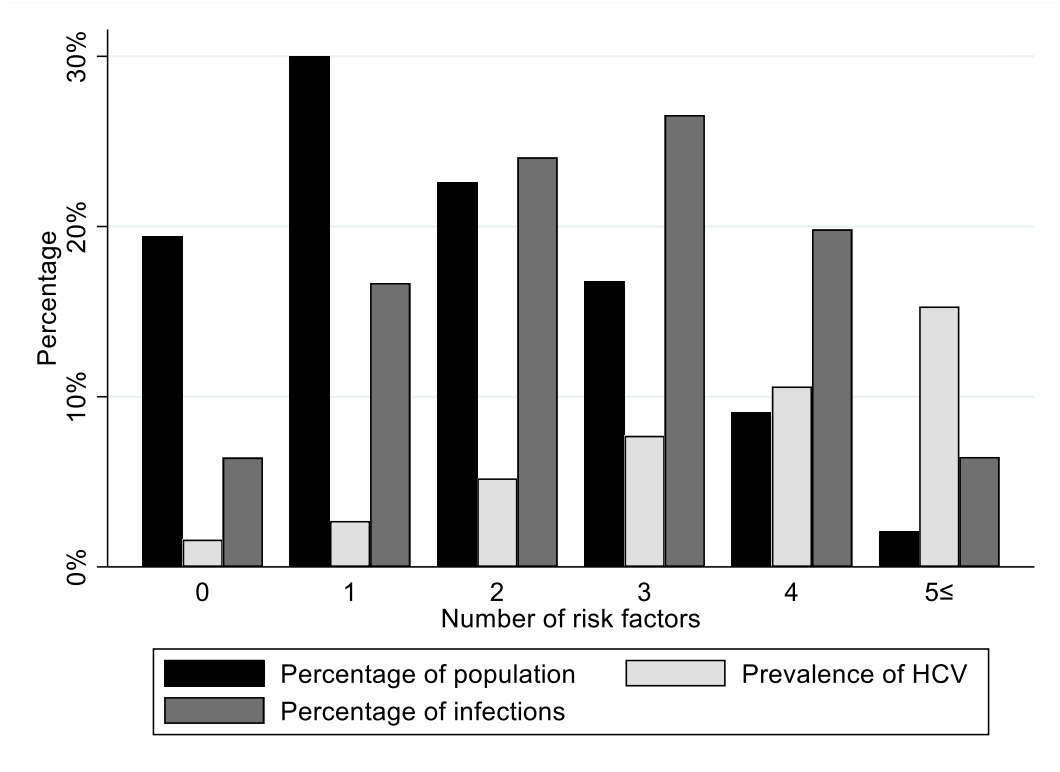
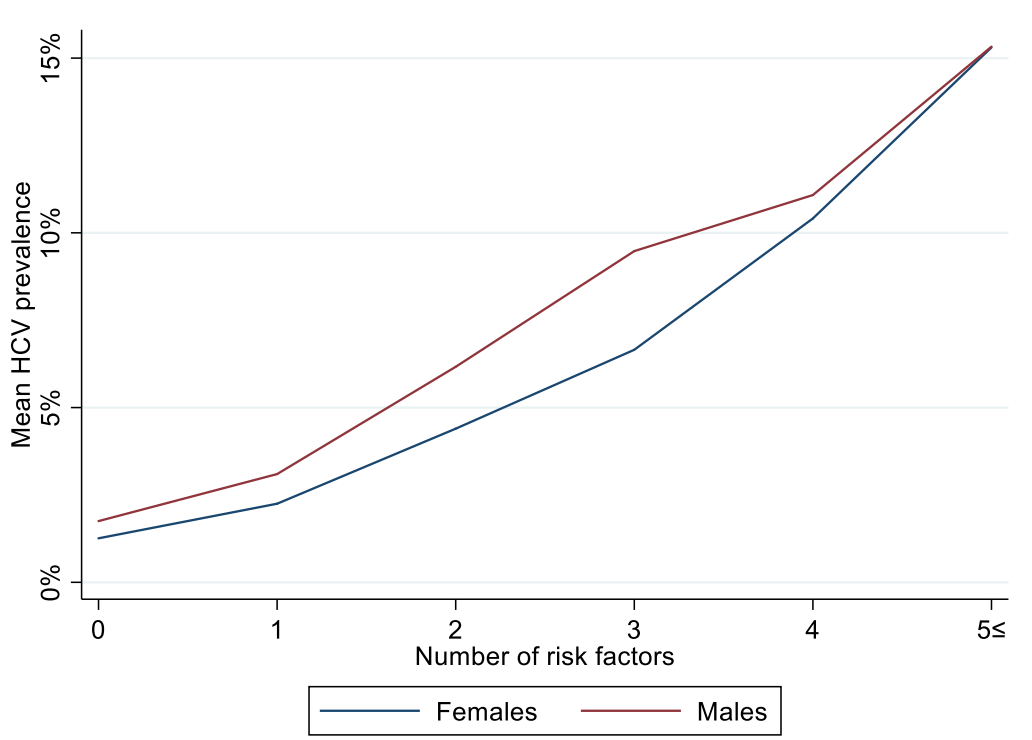


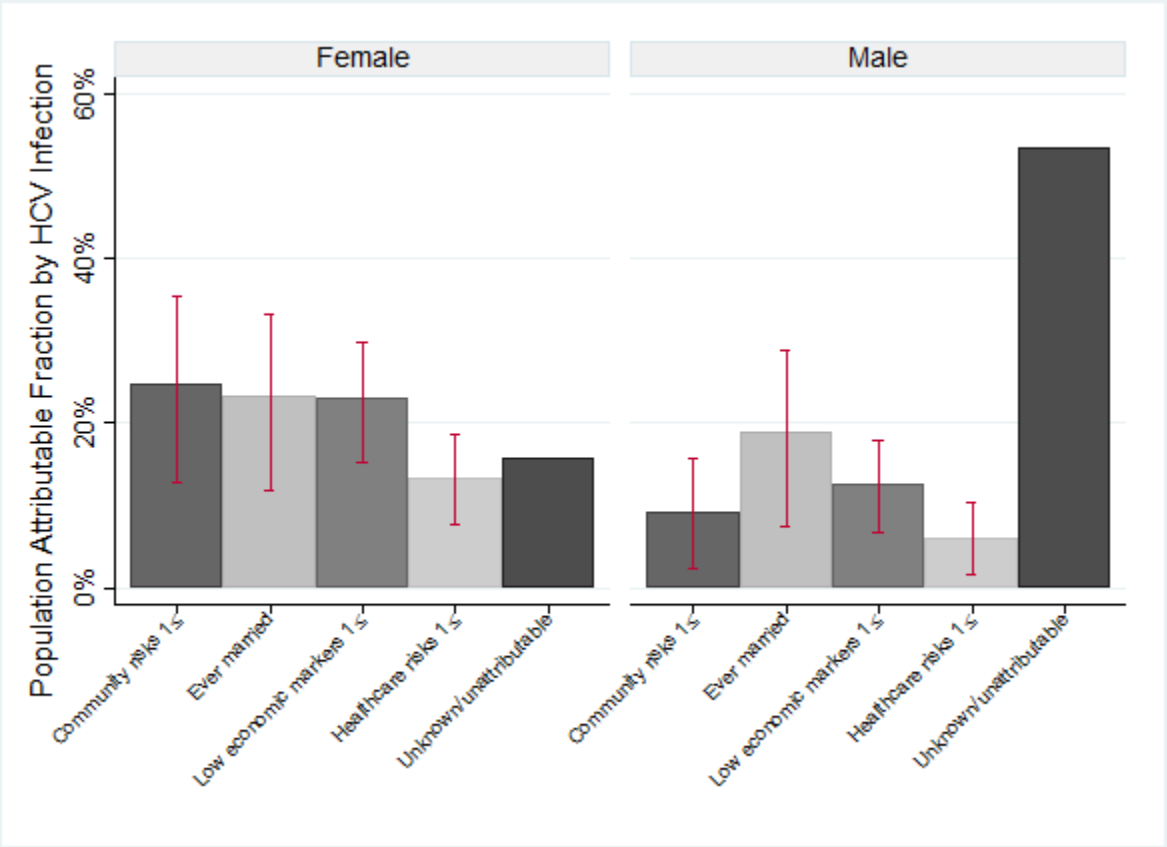
Figure 4.5: Mean HCV antibody prevalence by number of risk factors, by sex.



4.3.6. Population attributable fraction of HCV prevalence due to different exposures and risk factors

Figure 4.6 shows most HCV infections were not attributable to an identified risk factor/exposure. A greater proportion of HCV infections among females, 38% compared to 15% of males, were attributable to either a community or healthcare exposure, with community factors accounting for a greater proportion of HCV infections among both females and males. The PAFs suggest that prevention of exposure to community risks could potentially reduce HCV prevalence by 25% (95% CI: 13, 35%) and 9% (95% CI: 2, 16%) in females and males, respectively. In contrast, prevention of exposure to healthcare risks could potentially reduce HCV prevalence by 13% (95% CI: 8, 19%) in females and 6% (95% CI: 2, 10%) in males. Among both females and males, a high proportion of HCV appeared to be attributable to the exposures ever being married (23% and 19%, respectively) and low socio-economic status (23% and 13%, respectively).

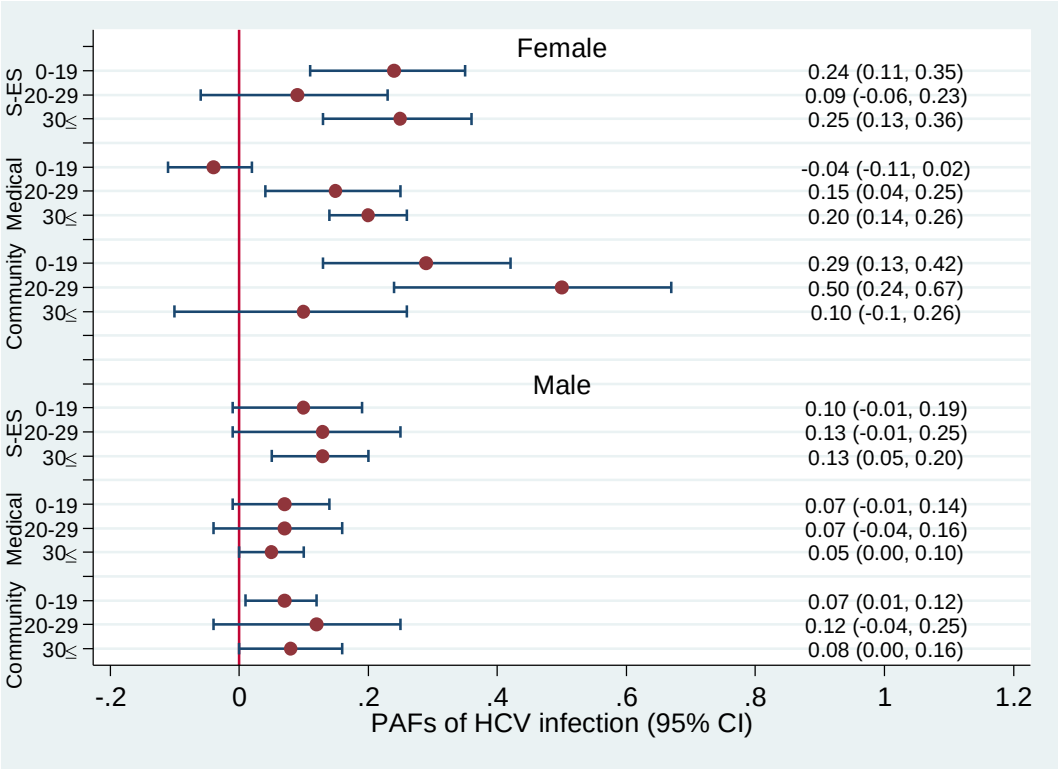
Figure 4.6: Population attributable fraction of HCV infection due to community and healthcare risks.



The PAFs for the grouped risk factor analyses stratified by age and sex can be seen in figure 4.7. For males of all ages socio-economic status appeared to be the most important in this analysis, with higher PAFs than for the other risk domains – 10%, 13%, and 13% for those aged 0-19, 20-29, and ≥30, respectively.

For the females aged 0-19, community risks and socio-economic status risks were both important predictors of HCV and accounted for 29% and 24% of the population attributable risk of HCV, respectively. Community risks accounted for half of the population attributable risk of HCV in females aged 20-29. Medical and socio-economic status risks were important HCV risk factors and accounted for 20% and 25% of the population attributable risk, respectively, for females aged ≥30 years.

Figure 4.7: Trends in PAFs of HCV infection by age for community, medical, and S-ES risk (presence versus absence), stratified by sex.



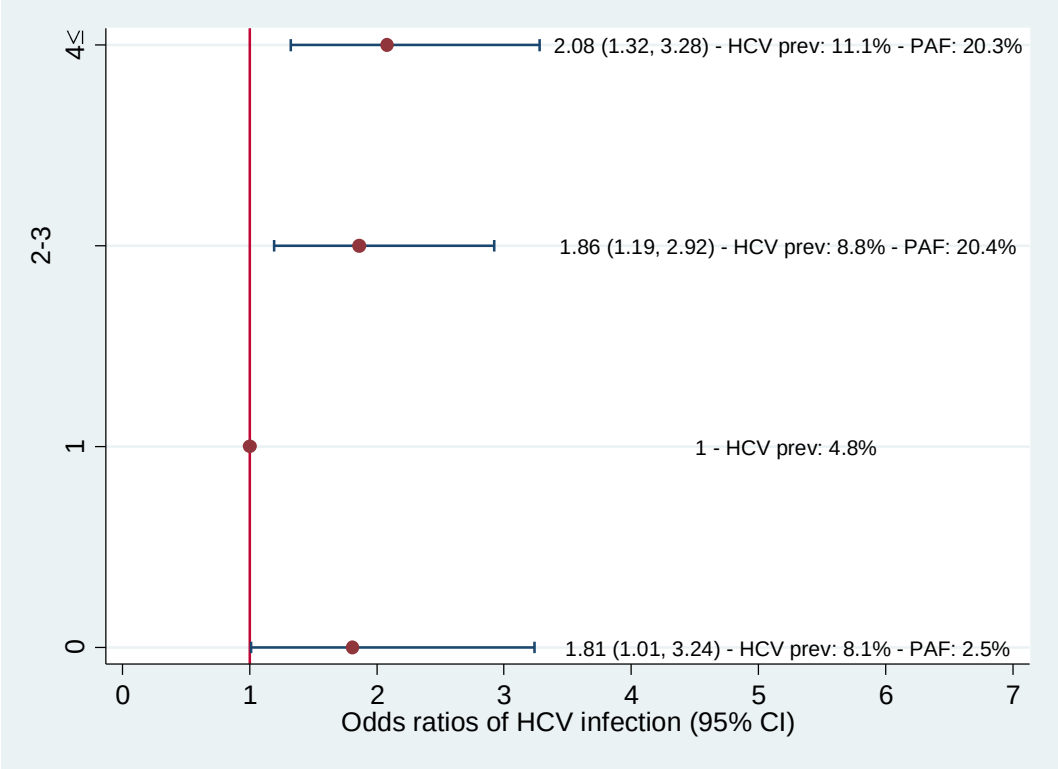
S-ES: socio-economic status

4.3.7. Association of childbirth with HCV

There were 5,556 women categorised in the survey as wives that were aged 20-59 years old. There was an increase in HCV infection prevalence associated with the number of children; linear trend, aOR per child 1.06 (95% CI: 1.01, 1.11). Figure 4.8 shows that being a childless wife was associated with having a higher risk of HCV than those with one child, aOR 1.81 (95% CI: 1.01, 3.24). The aOR of HCV for wives with 2-3 and ≥4 children compared to those with one child was 1.86 (95% CI: 1.19, 2.92) and 2.08 (95% CI: 1.32, 3.28), respectively. I repeated this analysis stratifying by the wives aged 20-29 (N=1,167) and those aged 30-59 (N=4,399), figure 4.9. The same associations observed in figure 4.10 with childless wives and women with 2-3 or ≥4 children having higher risk than those with one child were also seen here and appeared stronger in the younger women. The aOR of HCV for wives aged 20-29 years with 2-3 and ≥4

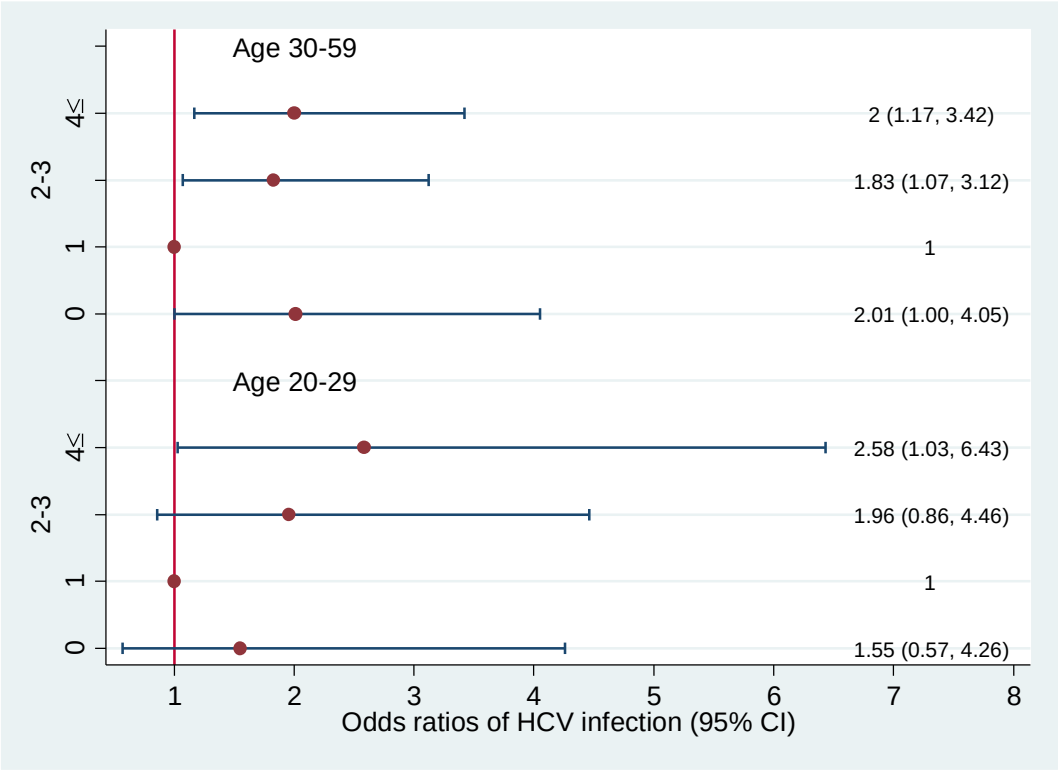
children compared to those with one child was 1.96 (95% CI: 0.86, 4.46) and 2.58 (95% CI: 1.03, 6.43), respectively, and for wives aged 30-59 years the aOR was 1.83 (95% CI: 1.07, 3.12) and 2.00 (95% CI: 1.17, 3.42) for the same comparison. The prevalence of HCV amongst the wives aged 20-59 was 7% in those aged 20-29 and approximately 10% (30-39: 10.0%, 40-49: 9.6%, 50-59: 9.8%) in those aged 30-59. This analysis was repeated in men aged 20-59, by assigning the childbirths of wives to husbands, and no association was found between childbirths and HCV: 0 childbirths (versus 1) aOR 0.94 (95% CI: 0.55, 1.59), 2-3 childbirths (versus 1) aOR 0.86 (95% CI: 0.59, 1.25), and ≥4 childbirths (versus 1) aOR 1.29 (95% CI: 0.88, 1.89).

Figure 4.8: Association of number of children with odds of HCV infection for wives, adjusted for age, province, and community, medical, and S-ES risks.



S-ES: socio-economic status

Figure 4.9: Association of number of children with odds of HCV infection for women of different ages (20-29 and 30-59 years), adjusted for province and community, medical, and S-ES risks.



S-ES: socio-economic status

4.3.8. Variables associated with syringe re-use

Table 4.7 shows the associations between syringe re-use and socio-economic status, as well as other demographic variables. The analysis found that those with low socio-economic status had higher odds that the previous medical injection they received was with a re-used syringe, aOR 1.08 (95% CI: 1.02, 1.16). Increasing age was positively associated with syringe re-use, whilst males were less likely to have received their last medical injection from a re-used syringe, aOR 0.91 (95% CI: 0.87, 0.95). Odds of syringe re-use varied by province.

Table 4.7: Unadjusted and adjusted ORs that the previous medical injection received was with a re-used syringe.

	Odds ratios (95% Confidence intervals)	
Risk factor	**Unadjusted**	**Adjusted**
Low S-ES status (vs high)	1.69 (1.61, 1.78)	1.08 (1.02, 1.16)
Male (vs female)	0.93 (0.89, 0.96)	0.91 (0.87, 0.95)
Age 0-19 years	0.08 (0.07, 0.08)	0.07 (0.06, 0.07)
Age 20-29 years	1	1
Age 30-39 years	1.17 (1.09, 1.27)	1.16 (1.07, 1.25)
Age 40-49 years	1.23 (1.13, 1.33)	1.21 (1.11, 1.31)
Age 50-59 years	1.33 (1.22, 1.45)	1.26 (1.15, 1.38)
Age ≥60 years	1.19 (1.09, 1.31)	1.19 (1.09, 1.31)
Punjab (Province)	1	1
Sindh	1.75 (1.62, 1.90)	2.35 (2.10, 2.64)
Baluchistan	1.97 (1.83, 2.12)	2.82 (2.57, 3.09)
North West Frontier	1.46 (1.34, 1.60)	1.93 (1.72, 2.16)

S-ES: socio-economic status

4.4. Discussion

4.4.1. Main findings

My findings identified healthcare associated exposures, including childbirth, as an important source of risk associated with HCV infection in Pakistan. In addition, these findings also suggest that various community risk factors/exposures, low socio-economic status, and marriage are associated with increased risk of HCV infection in the country. I estimated that the risk of HCV infection increases with cumulative lifetime healthcare exposures and accounts for 13% of female and 6% of male infections, whereas community exposures and low socio-economic status together account for over 20% and 10% of infections in females and males, respectively. The associations between these grouped variables (community, medical, and socio-economic risks) varied with age as well as sex, possibly explained by changing behaviours and improving healthcare practices that would be more noticeable amongst the younger age groups.

Marriage also emerged as an important surrogate marker of risk for both sexes, accounting for about 20% of all prevalent infections. The factors in marriage that contribute to HCV infection in Pakistan need additional study. Possible explanations could be shared practices or activities not recorded in the survey, or household transmission risks specific to the married couple, that are not specific to other members of the household. There is some evidence of transmission of HCV through sex, however this has mostly been anal sex between men who have sex with men(106, 377).

Unrecognised or unidentified risk factors beyond those associated with marriage, may also play an important role in transmission, as demonstrated by the large proportion of infections not attributable to either community or healthcare exposures identified in this survey. One potential important contributor could be injection drug use, which is a well-documented risk factor for HCV transmission, and is more prevalent in men than women(77). This could explain why more of the PAF for HCV was unaccounted for by the other variables in the model for males compared to females. Injecting drug users have a very high prevalence of HCV infection(6, 9, 164, 268). Of those surveyed, 0.1% responded that they had a history of injecting drug use, however, this could be under-reported due to stigma(77). Additionally, medical injections may

be more important than this analysis suggests; there was a high prevalence of receiving medical injections in the population, amongst both HCV exposed and unexposed individuals, limiting the degree to which the association could be ascertained.

4.4.2. Strengths and limitations

This study was based on a very large sample size which included children as well as adults. The results should be generalisable to the population of Pakistan as data were gathered from 100 districts in four provinces. However, the risk factor/exposure questions were limited in scope, often asking whether behaviours had ever occurred, which may have curtailed the degree to which elevated risk could be ascribed to them. HCV is a chronic condition and thus infection could have resulted throughout the lifetime of the study subject, further limiting the ability to associate recent exposures with infection. I was unable to determine why marriage and low socio-economic status were associated with increased prevalence of HCV infection – they may be surrogate markers for risk factors on which data were not available, or they could possibly be markers for shared healthcare utilisation and other behaviours. I also lacked direct data on the number of childbirths amongst females, or where the births occurred, for example, home or facility-based deliveries, and what type of delivery was performed, which limited the scope of the analyses on this risk factor. My method for measuring the number of childbirths is likely to underestimate the total number as some children will have died or left home; however, it should still be a useful proxy measure for the number of childbirths that a woman has had. The survey did not enquire about female genital mutilation or male circumcision, both of which could result in parenteral exposures(16, 187, 281). It is possible that risk associated with community risk factors may have been overestimated, as accurate attribution of risk to specific medical/healthcare interventions to a chronic infection such as HCV may not reflect the risk of specific exposures. This is particularly the case for exposures such as medical injections that are common in the population(175). As with all self-report surveys, there are likely to be problems with recall that can potentially bias the results. The nature of how the survey was administered could also have biased the answers that were given, particularly for injecting drug use.

Anti-HCV prevalence was used to determine associations with HCV infection because testing for current HCV infection (eg. PCR testing for presence of HCV RNA) was not performed. Further, I could not determine acute vs. chronic HCV infection; very few studies have assessed risk factors for recent, acute, or incident HCV infections amongst the general population(117, 182, 254, 275). This limits the degree to which I could determine current risk factors for HCV transmission as individuals with HCV antibodies may have been infected in the distant past or more recently. Importantly, this analysis found similar associations with HCV prevalence in younger and older individuals suggesting similar risk factors may exist now as in the past. One exception was the number of medical injections, which was only associated with HCV infection among study subjects aged over 30 years. From the data I cannot determine whether this is because cumulative exposure is more important or there has been a reduction in the risk due to medical injections in recent years(283). Despite an estimated reduction in the re-use of medical injections for every region globally(282), the 2018/2019 HIV outbreak in Kot Imrana, Pakistan, shows medical injections administered by "quacks" are likely still an issue for the transmission of bloodborne viruses, although in that example it was not possible to determine whether or not the infections could also have occurred through barbering or sexual transmission(386).

The main limitation of the study is the inability to accurately ascertain the extent of unsafe medical injections on the HCV epidemic in Pakistan. Much literature points to this as a major cause of HCV infection in Pakistan(13, 192, 256), however, this study can only report on the association between patterns of recent medical injection use and HCV infection. The WHO interventions to increase the use of sterilised needles are thought to have been effective(283, 398, 401) but this study cannot differentiate if infections occurred 20-years ago when the use of unclean injections was more prevalent(282, 296). Investigations into these associations are further hindered by the very high prevalence of injections for medical purposes in Pakistan in general(175), and the likely correlation between being ill, possibly from a previous HCV infection, and receiving these injections – a chicken and egg scenario. Although the type of syringe last used (new, re-used, don't know) was recorded, the survey does not contain information on the provider of the medical injections. My next chapter shows that this could be an important risk factor in some settings, with the type of healthcare provider being associated with different prevalences of HCV, likely due to different practices around use of unsterilised injecting equipment. This is perhaps a more important variable to have access to than the

quantity of medical injections, as a single unsterilised medical injection poses far more risk for transmitting HCV than hundreds of sterilised medical injections. For those aged over 30 years I found a protective effect for the last medical injection received being with a re-used syringe. This finding may highlight the problem of recall bias, although it should be noted that in younger groups this trend was reversed.

Another limitation is the lack of weighting for the importance of each individual risk factor in the analysis looking at the association between HCV prevalence and the number of risk factors. However, these weights would differ by age and sex, which would make the results of a weighted analysis difficult to interpret. The method of determining socio-economic status is perhaps not accurate in all cases as it is based on the householder rather than on individuals within the household but is likely to be a good proxy. Although subgroup analyses were carried out, for which multiple testing could be an issue, the very large sample size in each group will mitigate this and the need to use p-value corrections such as the Bonferroni method(23).

4.4.3. Comparison with other studies

My findings are consistent with previous studies examining risk factors for HCV infection in Pakistan(9, 29, 146, 164, 176, 194). In agreement with some studies, I found the importance of healthcare and community exposures for HCV transmission, including medical injections, childbirth, going to the barber, and ear/nose piercing(31, 176, 194, 222, 244, 280, 318, 355, 356). However, not all studies are in agreement, and some did not find an association with ear/nose piercing(6, 9, 29, 164, 173, 176), barbering or medical injections(6, 164), although these were much smaller surveys. Another study on women in Pakistan found that higher socio-economic status was associated with a higher proportion of injections received using a new syringe, as opposed to re-use(177). This is one of the possible explanations of the protective association of socio-economic status on HCV infection that I found and was confirmed in our dataset. This variable could also be a marker of accessing better quality health care which could also have a similar effect on reducing HCV risk. Therefore, socio-economic status may be masking medical risk factors for HCV transmission.

As found in other studies in Pakistan and elsewhere(8, 123, 134, 139, 183, 275), marriage is associated with HCV infection in both sexes. The reasons for this are uncertain, with some studies suggesting sexual HCV transmission or shared use of personal items(134, 139). For females in this study, the dominant exposures included ear and nose piercing, while a separate, restricted analysis also found childbirth to be an important exposure, possibly due to parenteral exposures(193). For almost every female in Pakistan, ear and nose piercing is a cultural ritual which is undertaken in very early years of life (<5 years)(115). Contact with barbers was associated with HCV infection among males. Barbering may be an important risk exposure among children, as well as adults, as every child (both male and female) undergoes head shaving around seven days of age(190). Also, most male children undergo circumcision, which is generally carried out by barbers in rural areas, but less so in urban areas(12).

Importantly for planning screening interventions, the cumulative number of risk factor exposures reported by an individual was highly predictive of HCV infection, with the sero-prevalence of HCV exceeding 10% among individuals with four exposures, and 15% in those with five or more. The effect was even more pronounced, 13% and 17% respectively, if they were from Punjab or Sindh.

4.4.4. Implications

My results highlight the importance of HCV prevention interventions not only targeting potential healthcare risks/exposures in Pakistan, but also community settings and family behaviours where exposures may occur. These are likely to include barbering and ear piercing, and family behaviours such as sharing personal items like razors and toothbrushes, and practices associated with childbirth(9, 29, 176, 318). More research is needed to better understand the main risk behaviours occurring in different settings. For instance, childbirth may be high-risk only in certain settings, or when specific obstetric or gynaecological procedures are involved(146, 292, 318). A recent meta-analysis found that caesarean section conferred a high-risk for HCV infection (OR=3.35)(92), and other studies have documented the risk of HCV infection to both mother and child after labour(35, 118, 134).

A number of educational interventions have been undertaken in Pakistan over the past decade to tackle community and general risk exposures such as barbering, tattooing, and body piercing(202, 298, 324, 325). For instance, in 2014/2015, the Health Foundation developed an HCV educational intervention in Karachi, Pakistan, that aimed to educate the general public on healthcare and community risk factors through health educator volunteers and electronic and print media(188). A similar intervention is being done in Azad Kashmir in Northern Pakistan(270). There is a need to better understand the effectiveness and impact of these interventions on practices and HCV transmission.

4.4.5. Conclusions

In summary, my results highlight the multitude of community and healthcare exposures that drive HCV transmission in Pakistan; similar risk factors for transmission have been identified in Egypt, another high prevalence setting(92, 130, 134, 275, 305). These findings underscore the urgent need for implementation of strategies to decrease HCV transmission in Pakistan and other countries with similar risk profiles. Treatment scale-up for HCV infection, with the new highly effective direct acting antivirals(101, 103), is planned in Pakistan, and many are already receiving treatment(60). The finding from the study that HCV infection is strongly associated with cumulative number of self-reported risk factors/exposures could help inform screening strategies to efficiently target individuals at highest risk for HCV infection. While scaling-up treatment is urgently needed to tackle the huge burden of HCV in Pakistan, policy makers should also remember the need for large-scale prevention interventions to curtail the continued transmission of HCV. Indeed, the low prevalence of HCV in many neighbouring countries(19, 65) suggests the required changes in behaviour are possible with suitable interventions, including education campaigns, to improve knowledge on HCV transmission risks. These education campaigns need to be tailored to the local situation, which may require further research to identify the reasons why marriage, childbirth, and socio-economic status are associated with increased HCV risk in Pakistan.

CHAPTER 5. THE BURDEN OF HEPATITIS C VIRUS INFECTION IN PUNJAB, INDIA: A POPULATION-BASED SEROSURVEY

The work in this chapter was done in collaboration with Ajit Sood, Anil Suryaprasad, Subodh Kanchi, Vandana Midha, Monique A Foster, Eddas Bennett, Saleem Kamili, Fernando Alvarez-Bognar, Shaun Shadaker, Vijay Surlikar, Ravinder Garg, Parmod Mittal, Suresh Sharma, Margaret T May, Peter Vickerman, and Francisco Averhoff, and is published in PLOS ONE(346).

5.1. Introduction

In order to establish effective hepatitis C virus (HCV) prevention and treatment programs, there is a need to understand the epidemiology and burden of disease in the country or community. However, such data are lacking in many countries, particularly in low- and middle-income countries which shoulder most of the burden(124). In India, population-based studies on HCV infection prevalence are lacking and the epidemiology is not well understood. Some studies from India suggest the HCV prevalence may be low, however, there are significant variations within regions and sub-populations, with some studies demonstrating very high prevalence rates(262, 333). Despite a recent systematic review(121), the HCV burden in India is poorly described because of a paucity of community level data(121).

Due to the high cost of direct acting antivirals (DAAs), it has been postulated that for some countries treating all HCV-infected persons would cost more than their total expenditure on pharmaceuticals(171). However, India produces the bulk of the world's generic licensed DAAs, and prices are lower than most countries, removing this barrier to treatment access(220). In 2016, the Indian state of Punjab launched a program to provide HCV treatment free of charge(360).

Punjab is a state in Northern India with an estimated population of around 28 million people(358). A survey conducted in one district of Punjab in 2003 found a 5% anti-HCV positive rate; in that study, infection was associated with reuse of needles and syringes, history of surgery, and history of dental extraction(344). Elevated rates of HCV infection have also been identified among high risk populations (eg. people who inject drugs [PWID]) in Punjab(179, 278), which may reflect the growing epidemic of injection drug use, a high-risk behaviour for HCV infection(359). Epidemiological assessment of the burden of disease and characteristics and behaviours associated with HCV infection in the state are essential for public health planning strategies to combat this disease.

In chapter 4, I investigated the associations of risk factors for HCV infection in Pakistan, which neighbours Punjab, India. Punjab also has a high anti-HCV prevalence, 4.9% (95% CI: 4.7%, 5.1%). I found in chapter 4 that a mixture of healthcare and community factors, such as medical injections and barbering, as well as low socio-economic status are associated with HCV antibody positivity. In this chapter, I aim to assess the prevalence of HCV infection in Punjab, India, and, similarly to chapter 4, identify behaviours and characteristics associated with HCV antibody positivity. I also compare the results with those found in the previous chapter.

5.2. Materials and methods

The serosurvey used in this chapter was designed by my collaborators. I performed all statistical analyses.

5.2.1. Sample design

A cross-sectional seroprevalence survey was conducted in the state of Punjab, India, during October 2013 – April 2014. Punjab is divided into three major geographical areas, Doaba, Majha, and Malwa, which contain a total of 22 districts. The survey sample size was calculated to enable estimation of HCV prevalence among individuals age 5 years and older, using the statistical software PASS (NCSS, LLC. 2011 Kaysville, Utah, USA). For an expected HCV prevalence of 5% with a 95% confidence interval (CI) of 4-6%, the effective sample size was estimated to include 1,924 households. Those designing the study assumed a design effect of 2 (how different a survey's expected sampling error is from the sampling error expected with simple random sampling(242)) and an overall response rate of 70%, with a target sample size of 5,500 individuals.

The study included testing for past and current HCV infection, past infections with hepatitis A virus and hepatitis E virus, and past or current infection with hepatitis B virus (HBV). This chapter, and thesis, is only concerned with the results for HCV. The sample size of 5,500 individuals was expected to be large enough to produce combined estimates with relative standard errors of 10-20%. For a stratified analysis, a minimum sample size of 1,000 per strata (eg. stratification based on rural/urban dwelling) was expected to produce estimates with relative standard errors of 25% or less. Estimates based on relative standard errors >25% are considered unreliable(27).

The survey used a multi-stage stratified cluster sampling design using 2011 Punjab Census data(358), and 10 of the 22 districts in Punjab were selected with probability proportionate to size. In rural areas, 22 sub districts and 87 villages were selected proportionate to size, and 813 households were systematically selected in groups of five. To ensure the selection of a sufficient number of households in rural areas, villages with fewer than five households were excluded,

and villages with 5-49 households were combined with neighbouring villages, for a minimum of 50 households per sampling unit. In urban areas, 13 sub districts and 41 wards were selected proportionate to size; 1 census enumeration block of 150-200 households was randomly selected per ward; and 586 households were systematically selected in groups of five. For large sampling units, villages and census enumeration blocks with 500 or more households were divided into three or more segments and two segments were selected proportionate to size.

All household residents and guests 5 years of age and older who stayed at the household the previous night were eligible to participate in the study. Selected adults aged ≥18 years who provided informed consent were included. Children aged 5-17 years who provided assent and for whom informed parental/guardian consent was also given were included. Pregnant women were included, since participation in the study did not pose any risk to the mother or her unborn child. Individuals under 5 years of age and those who did not provide consent or assent were not included. No replacement was made if selected household was not available during data collection.

5.2.2. Data collection

Trained survey teams consisting of a doctor, a phlebotomist, a nurse, and a social worker visited selected households and administered the survey questionnaire, after obtaining informed consent and assent from children willing to participate. The study questionnaire was administered as a face-to-face interview and inquired about socio-demographic data, medical history, lifestyle information, obstetric history (if applicable), and potential exposures to HCV, including healthcare and lifestyle associated exposures. Each completed questionnaire was reviewed in the field by the team doctor, and if inconsistencies or gaps were identified, an attempt to correct or fill in the missing information was made by revisiting the surveyed individual before leaving the cluster. Each completed interview was labelled with a bar code with a unique identifier.

5.2.3. Sample storage and testing

After completing the interview, a blood sample of approximately 16ml was drawn in a serum separator tube and labelled with a barcode matching the interview form completed by the study subject. Within one hour of collection, the sample was centrifuged for 15 minutes at 3,000 revolutions per minute. Separated serum was pipetted into 2ml cryovials, which were also labelled with bar codes matching the study subjects. Up to eight aliquots of sample per subject were prepared and frozen at -80C. Specimens were shipped every 2 weeks to a central laboratory (Oncquest Laboratories Ltd) in Delhi for testing. All samples were tested for anti-HCV (Vitros Immunodiagnostic Anti-HCV, Johnson and Johnson Co., New Brunswick, NJ, USA) and all anti-HCV positive samples were tested for HCV RNA (COBAS® TaqMan® HCV Test, Roche, Indianapolis, IN, USA). All HCV RNA positive samples were genotyped by Linear Array HCV genotyping test (Roche, Indianapolis, IN, USA). The sensitivity and specificity of the anti-HCV test used were 100% and 96.5%, respectively(196), and for the HCV RNA test were 100% and 95%, respectively(116). Survey participants who tested positive for anti-HCV were considered infected with HCV, regardless of HCV RNA results. Survey participants who tested positive for anti-HCV and HCV RNA were considered to have current infection, and those that tested anti-HCV positive and HCV RNA negative were considered to have past infection. Specimens were also tested for hepatitis A virus, HBV, and hepatitis E virus markers of infection (methods and results not described in this thesis). Unused blood was disposed of as per healthcare waste management guidelines and all specimens were destroyed following completion of the study.

5.2.4. Counselling and notification of test results

For consenting participants, pre-test counselling and educational brochures on HCV transmission and prevention were administered prior to interview and venepuncture. Study participants were notified of their test results for HCV, HBV, hepatitis A virus, and hepatitis E virus infection or immunity by telephone and mail within three weeks of the interview date. Patients found to have current (active) HBV or HCV infection were offered post-test counselling

by appointment. All participants were counselled about measures to prevent the risk of transmission of the various forms of viral hepatitis.

5.2.5. Ethical considerations

The protocol for this study underwent approval from the Institutional Review Board (IRB) at Dayanand Medical College, Ludhiana, and the Merck Investigator Initiated Study Protocol-Review Committee (MISP-RC). Participation was voluntary and confidentiality was strictly adhered to during the survey. Written consent was documented by the study subject's dated signature or thumbprint on a consent form along with the dated signature of the person who conducted the consent discussion. A copy of the consent form was given to the subject prior to participating in the survey. Consent forms were available in English, Punjabi, and Hindi. If the subject was illiterate, a witness was present during the entire informed consent reading and discussion. Afterward, the subjects signed and dated the consent if literate, or a thumb impression was taken. The witness also signed and dated the consent form along with the study staff who read and discussed the consent. Children ≥5 years and <18 years of age provided assent in addition to having parental permission.

5.2.6. Statistical methods

My analyses of the survey data were weighted according to the population sizes of the wards and villages estimated from the 2011 population census. This weighting was stratified by urban/rural status to account for expected differences. The HCV prevalence was estimated for the state overall, by urban/rural residence, and by district. I used a chi-squared test to examine whether the proportion of HCV RNA positive patients with each genotype differed by district. Participant characteristics and HCV risk factors were tabulated against the percentage of individuals with each characteristic/risk factor testing positive for anti-HCV and those testing positive for HCV RNA. The variables included in these tabulations were district, age-group (5-18, 19-29, 30-45, 46-60, >60), sex, urban/rural status, household income in rupees (<20,000, ≥20,000), education status (never educated/primary education, middle/secondary,

graduate/above), the number of injections received in the last 6 months (0, 1-3, 4-8, >8), who administered the last injection received (Medical Doctor, Registered Nurse/Medical Practitioner, Other/Unknown (including chemists and unlicensed practitioners), the number of lifetime blood donations (0, 1-3, 4-6, >7), the number of blood transfusions received (0, 1-3, >3), if ever received a permanent tattoo, the number of childbirths, whether they have a history of surgery, whether they have a history of dental surgery, whether they have ever received a body piercing, and whether they shave at the barber, if they have ever used injectable drugs, or had ever received renal dialysis. Proportions and numbers presented in the tabulations were weighted (as mentioned at the start of this paragraph) to represent the population surveyed. Tabulations were stratified by urban/rural status and by gender.

The variables investigated in the paper this chapter is based on were selected a priori. However, for comparability with chapter 4 the analyses presented in this chapter were additionally adjusted for the number of childbirths, whether they have a history of surgery, whether they have a history of dental surgery, whether they have ever received a body piercing, and whether they shave at the barber.

5.2.7. Association of HCV with patient characteristics and risk factors

I estimated the association of patient characteristics and HCV risk factors with HCV status using weighted logistic regression models for the total survey population, stratified by urban/rural status, and clustered by household. Age, the number of injections received in the last 6 months, the number of times the person had donated blood, and the number of blood transfusions received were included in models as continuous variables. Results are presented as weighted unadjusted and mutually adjusted odds ratios (OR) of having a positive anti-HCV test, with 95% confidence intervals (CI). I also estimated the association of the year of the first blood transfusion received (grouped as before 2002, 2002 or later year, year unknown, and no blood transfusions received; of note, blood bank testing for HBV and HCV became mandatory in Punjab by law in 2002(264)) with HCV status. I used the same mutually adjusted model as above, but instead of including the number of blood transfusions I included the year of first

receiving a blood transfusion. I did not include the variables (dialysis, injecting drug use) with very few observations in the regression models in order to increase power.

5.2.8. Sensitivity analyses

A sensitivity analysis excluded participants 18 years of age or under because some risk factors only applied to adults. Another sensitivity analysis only included participants aged 40-59 years of age to investigate whether risk factors were different for the two highest prevalence age groups.

5.2.9. Cumulative risk factors

I examined the number of injections (categorised: 0, 1-3, 4-8, >8) received in the last 6 months by anti-HCV prevalence. I examined the relationship of cumulative number of different types of potential exposures found to be associated with anti-HCV prevalence by univariable analysis (including having ever received a blood transfusion, having ever received surgery, having ever received dental surgery, having received a medical injection within the last 6 months, and whether they shave at a barber) and testing positive for anti-HCV. I used logistic regression to estimate the adjusted OR (aOR) of anti-HCV positivity for number of risk factors (1, 2-3) compared with no risk factors.

5.3. Results

5.3.1. Serosurvey participant characteristics

A total of 5,548 individuals agreed to participate in the serosurvey and completed the questionnaire. However, 5 lacked HCV testing results and were excluded, resulting in 5,543 subjects for inclusion in the analyses. Data is unavailable on how many individuals refused to participate. The median age of the sample was 35 years (interquartile range: 21, 50) while the largest age group was participants aged 5-18 years (table 5.1). There were more women (53.8%)

than men (46.2%) that participated in the serosurvey, and 62.4% of all participants resided in rural areas (table 5.1). Of the serosurvey participants, 12.5% attended graduate school, and 81.9% lived in households with an income of less than 20,000 Indian rupees (about 300 US dollars), which is below the national average of 27,857 Indian rupees(358) (table 5.1).

Examining potential exposures for HCV infection, 34.8% of participants had received one or more medical injections in the previous 6 months in the weighted analysis. When asked who administered their last medical injection, 20.4% identified a medical doctor and 56.9% identified a registered nurse or registered medical practitioner (eg. medical care provider not having the qualifications/training of a medical doctor). For those who had received at least one medical injection in the last 6 months, 24% received it from a medical doctor, 71% from a registered nurse or registered medical practitioner, and 5% from other sources (eg. chemist or pharmacist, unlicensed practitioner, or did not specify). Of all participants, 6.5% stated they had received at least one blood transfusion. Additionally, 8.6% of patients had received a permanent tattoo, while few (0.1%) participants admitted to ever using injectable drugs. The median number of childbirths for the females surveyed was 2 (interquartile range: 0-3). Body piercings were mostly among females, with 96% of females having one but only 6% of males. All participants reporting shaving at the barber were male.

5.3.2. HCV prevalence

Overall, of the 5,543 persons tested for hepatitis C, 3.6% (95% CI: 3.0%, 4.2%) tested positive for anti-HCV, and 2.6% (95% CI: 2.0%, 3.1%) tested positive for HCV RNA. Among the 138 that tested positive for RNA, 130 were successfully tested for genotype: the majority were classified as genotype 3 (61.2%), followed by genotype 1 (27.5%) and genotype 4 (11.3%). No participants in the serosurvey were found to have genotype 2. The proportions of RNA positive patients with each genotype differed by province (p=0.038). Anti-HCV prevalence was higher among rural residents [4.7% (95% CI: 3.8%, 5.7%)] than urban residents [1.6% (95% CI: 1.1%, 2.2%)] (table 5.1). The proportion of serosurvey participants testing positive for HCV antibodies differed by district, ranging from 1.1% in Gurdaspur to 9.0% in Moga (figure 5.1). However, different proportions of participants were sampled from rural and urban areas in each district

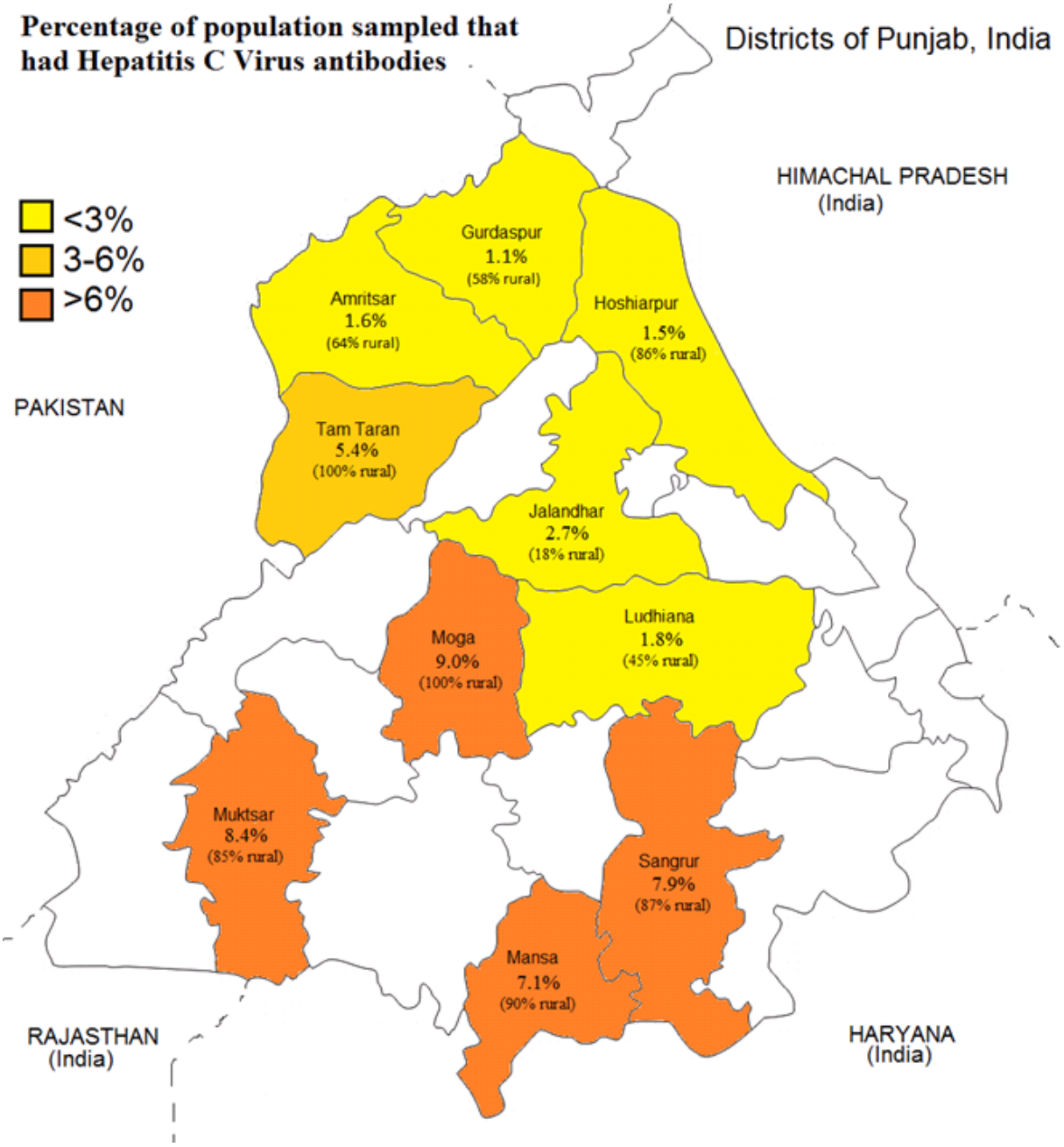
as this serosurvey was designed to estimate prevalence for Punjab as a whole, not to estimate district level prevalence.

Table 5.1: Participant demographic characteristics and prevalence of potential exposures and risk factors associated with HCV infection, with the percent testing anti-HCV positive and for HCV-RNA cells.

Variables	Unweighted Population	Weighted Population	% with positive anti-HCV (95% confidence intervals)	% with HCV RNA (95% confidence intervals)
Overall	5543	100%	3.6% (3.0%, 4.2%)	2.6% (2.0%, 3.1%)
Age Group (years)				
5-18	1107	20.2%	0.7% (0.1%, 1.2%)	0.4% (0.0%, 0.8%)
19-29	1024	18.3%	1.7% (0.8%, 2.5%)	1.2% (0.5%, 1.9%)
30-39	998	18.0%	4.3% (2.9%, 5.7%)	3.1% (1.8%, 4.3%)
40-49	870	15.7%	6.2% (4.4%, 8.0%)	4.7% (3.1%, 6.2%)
50-59	721	13.0%	5.8% (3.9%, 7.7%)	4.5% (2.7%, 6.2%)
≥60	823	14.9%	4.3% (2.7%, 5.8%)	2.7% (1.4%, 3.9%)
Sex				
Female	3005	53.8%	3.2% (2.5%, 3.9%)	2.3% (1.7%, 2.9%)
Male	2538	46.2%	4.0% (3.1%, 5.0%)	2.8% (2.1%, 3.6%)
Setting				
Urban	2083	37.6%	1.6% (1.1%, 2.2%)	1.0% (0.6%, 1.4%)
Rural	3460	62.4%	4.7% (3.8%, 5.7%)	3.5% (2.7%, 4.3%)
Household income (rupees)				
<20,000	4546	81.9%	3.8% (3.1%, 4.5%)	2.7% (2.1%, 3.3%)
≥20,000	997	18.1%	2.5% (1.2%, 3.7%)	1.9% (0.8%, 2.9%)
Education				
Never/Primary School	2114	37.7%	4.7% (3.6%, 5.8%)	3.8% (2.8%, 4.8%)
Middle/Secondary School	2735	49.8%	3.4% (2.6%, 4.1%)	2.1% (1.5%, 2.7%)
Graduate/Above	694	12.5%	1.1% (0.3%, 1.8%)	0.6% (0.1%, 1.2%)
No. injections in last 6 months				
0	3639	65.2%	3.1% (2.4%, 3.8%)	2.2% (1.7%, 2.8%)
1-3	1155	21.1%	3.8% (2.6%, 5.0%)	2.5% (1.6%, 3.4%)
4-8	461	8.3%	4.7% (2.5%, 6.9%)	3.7% (1.6%, 5.7%)
>8	288	5.4%	7.0% (3.5%, 10.4%)	5.0% (2.1%, 7.9%)
Last injection given by				
Medical Doctor	1149	20.4%	2.1% (1.2%, 2.9%)	1.3% (0.6%, 2.0%)
Registered Nurse/Medical	3090	56.9%	4.4% (3.6%, 5.2%)	3.3% (2.5%, 4.0%)
Other/Unknown	1304	22.7%	2.9% (2.9%, 4.0%)	1.9% (1.0%, 2.9%)

Variables	Unweighted Population	Weighted Population	% with positive anti-HCV (95% confidence intervals)	% with HCV RNA (95% confidence intervals)
Number of times blood donated				
0	4808	86.5%	3.6% (2.9%, 4.2%)	2.5% (1.9%, 3.0%)
1-3	528	9.8%	3.3% (1.5%, 5.1%)	3.2% (1.4%, 5.0%)
4-6	115	2.1%	4.6% (0.5%, 8.6%)	3.6% (0.0%, 7.3%)
≥7	92	1.7%	5.3% (0.2%, 10.3%)	2.4% (0.0%, 5.8%)
Number of transfusions received				
0	5175	93.6%	3.4% (2.8%, 4.0%)	2.4% (1.9%, 2.9%)
1-3	353	6.3%	5.9% (3.2%, 8.6%)	4.6% (2.2% (6.9%)
>3	15	0.2%	25.8% (0.0%, 53.7%)	25.8% (0.0%, 53.7%)
Number of childbirths				
0	3416	62.0%	3.4% (2.4%, 4.8%)	2.4% (1.6%, 3.6%)
1-2	1109	20.2%	3.6% (2.5%, 5.4%)	2.8% (1.9%, 4.2%)
3-4	809	14.2%	3.5% (2.2%, 5.4%)	2.3% (1.4%, 4.0%)
≥5	209	3.6%	6.2% (3.5%, 10.9%)	5.3% (2.8%, 9.9%)
Use of Injectable Drugs				
Yes	5	0.1%	25.1% (0.0%, 66.8%)	25.1% (0.0%, 66.8%)
No	5538	99.9%	3.6% (2.9%, 4.2%)	2.5% (2.0%, 3.1%)
Any dialysis				
Yes	26	0.4%	0.0% (0.0%, 0.0%)	NA
No	5517	99.5%	3.6% (3.0%, 4.2%)	2.6% (2.0%, 3.1%)
History of surgery				
Yes	2353	42.8%	4.4% (3.2%, 6.1%)	3.3% (2.3%, 4.6%)
No	3190	57.2%	2.9% (2.1%, 4.0%)	2.0% (1.4%, 3.0%)
History of dental surgery				
Yes	2173	39.5%	4.6% (3.4%, 6.3%)	3.4% (2.3%, 5.0%)
No	3370	60.5%	2.9% (2.1%, 4.0%)	2.0% (1.4%, 2.8%)
Received a permanent tattoo				
Yes	479	8.6%	5.2% (2.8%, 4.1%)	3.7% (1.9%, 5.4%)
No	5064	91.4%	3.4% (3.1%, 7.3%)	2.5% (1.9%, 3.0%)
Received a piercing				
Yes	3061	54.6%	3.3% (2.5%, 4.4%)	2.4% (1.7%, 3.2%)
No	2482	45.4%	3.9% (2.7%, 5.6%)	2.8% (1.8%, 4.3%)
Shaves at a barber				
Yes	1081	19.6%	4.9% (3.5%, 6.7%)	3.4% (2.2%, 5.1%)
No	4462	80.4%	3.3% (2.4%, 4.5%)	2.4% (1.6%, 3.4%)

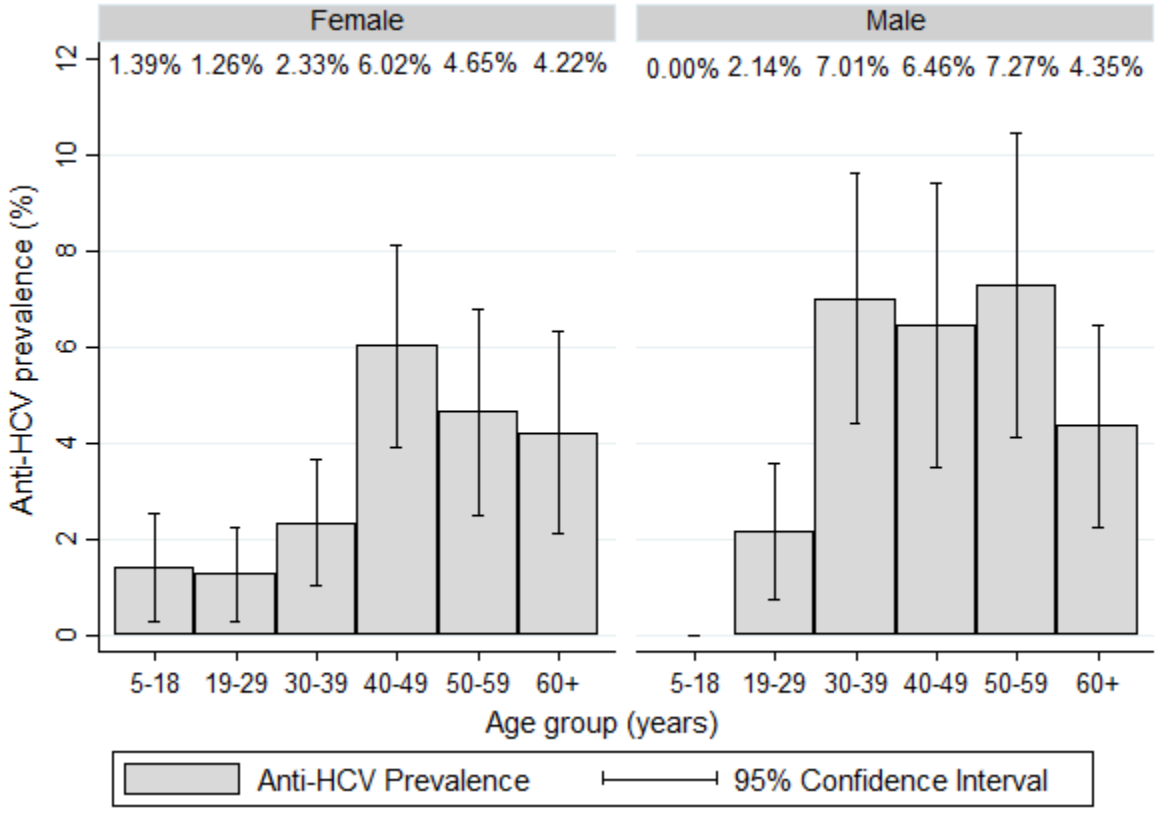
Figure 5.1: Percentage of participants sampled in each district that had HCV antibodies.



5.3.3. HCV prevalence by age

I found the anti-HCV prevalence increased with age up to the 40-49-year group where it peaked [6.6% (95% CI: 4.4%, 8.0%)] and then decreased with increasing age (table 5.1). Overall, anti-HCV prevalence among men [4.0% (95% CI: 3.1%, 5.0%)] and women [3.2% (95% CI: 2.5%, 3.9%)] was similar (table 5.1). When stratified by age, there were some differences in seroprevalence by age groups among men and women (figure 5.2). Men aged 30-39 had a higher anti-HCV prevalence (7.0%) than women aged 30-39 (2.3%), whilst males aged 5-18 had a lower prevalence (0.0%) than females aged 5-18 (1.4%).

Figure 5.2: Prevalence of HCV antibodies by age category and sex*.



*HCV prevalence for each age group is at the top of the figure. Whiskers indicate 95% confidence intervals.

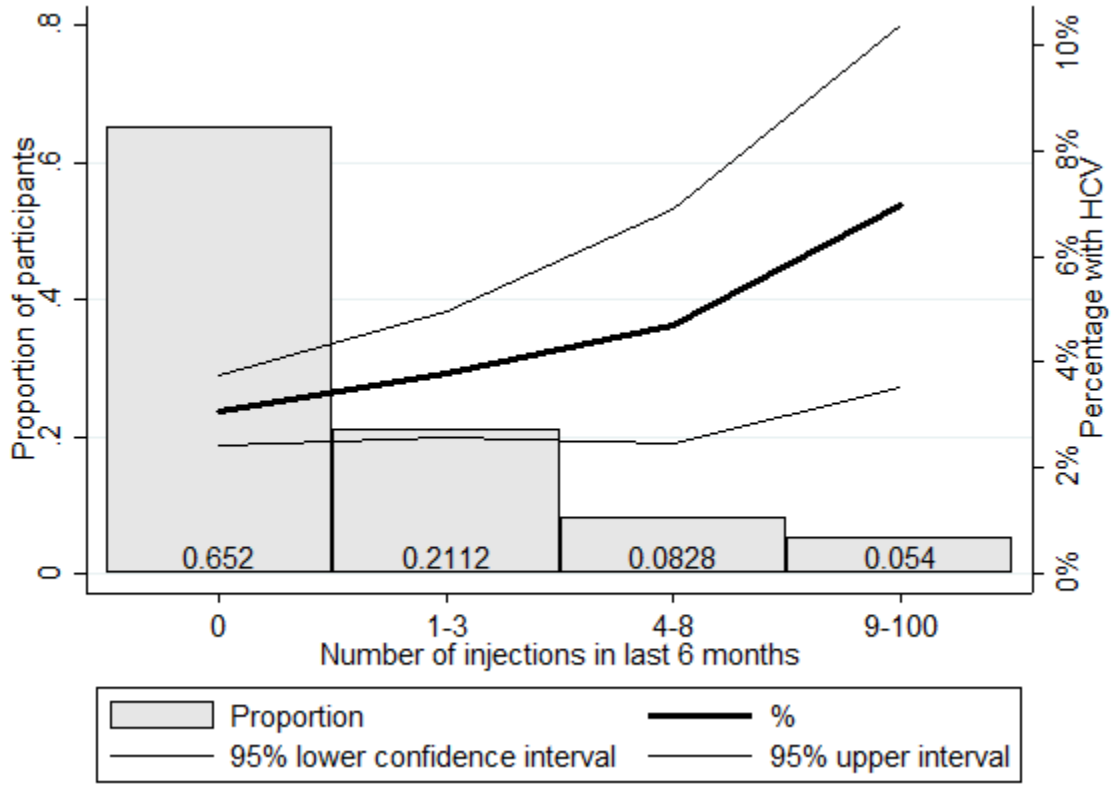
5.3.4. Associations of HCV with healthcare, community, and other variables

When I examined the prevalence of HCV antibody positivity by potential exposures and risk factors, I found that prevalences were higher as the number of injections received increased (see figure 5.3). Anti-HCV prevalences were highest for those whose last injection was administered by a nurse, registered medical practitioner, or other non–medical doctor, 4.4% (95% CI: 3.6%, 5.2%), compared with those receiving their last injection from a medical doctor, 2.1% (95% CI: 1.2%, 2.9%), or other/unknown, 2.9% (95% CI: 2.9%, 4.0%). Prevalences increased with the number of blood transfusions received, ranging from 3.4% (95% CI: 2.8%, 4.0%) for those that had received none, to 5.9% (95% CI: 3.2%, 8.6%) for those receiving 1-3 transfusions, up to 25.8% (95% CI: 0.0%, 53.7%) for the 15 participants with >3 blood transfusions. Women who had had 5 or more childbirths had an HCV prevalence of 6.2% (95% CI: 3.5%, 10.9%), whilst women who had had 3-4 children, 1-2 children, or people that had 0 children all had similar, lower HCV prevalences; 3.5% (95% CI: 2.2%, 5.4%), 3.6% (95% CI: 2.5%, 5.4%), and 3.4% (95% CI: 2.4%, 4.8%), respectively. Participants with a history of surgery had a higher HCV prevalence, 4.4% (95% CI: 3.2%, 6.1%), than those that had never had surgery, 2.9% (95% CI: 2.1%, 4.0%), whilst those with a history of dental surgery had a higher anti-HCV prevalence, 4.6% (95% CI: 3.4%, 6.3%), than those without, 2.9% (95% CI: 2.1%, 4.0%).

Anti-HCV prevalence decreased with increasing educational attainment, with a prevalence of 4.7% (95% CI: 3.6%, 5.8%) in those educated up to a primary school level or less, 3.4% (95% CI: 2.6%, 4.1%) prevalence among those with middle/secondary school education, and 1.1% (95% CI: 0.3%, 1.8%) prevalence for those with a "Graduate/above" level of education. Anti-HCV prevalence was lower among persons with higher household incomes (≥20,000 rupees), 2.5% (95% CI: 1.2%, 3.7%), than those with lower incomes, 3.8% (95% CI: 3.1%, 4.5%). HCV antibody prevalence was higher among persons who had received a permanent tattoo, 5.2% (95% CI: 2.8%, 4.1%) than those who had not, 3.4% (95% CI: 3.1%, 7.3%). Similarly, it was higher for people that go to a barber for shaving, 4.9% (95% CI: 3.5%, 6.7%), than those who do not 3.3% (95% CI: 2.4%, 4.5%). The prevalence was lower among those with a body piercing, 3.3% (95% CI: 2.5%, 4.4%), than those without, 3.9% (95% CI: 2.7%, 5.6%). There were no HCV infections among persons who had a history of receiving dialysis (table 5.1). However, the number persons with some of the exposures and risk factors, including dialysis (n=26) and injection

drug use (n=5), were small. The anti-HCV prevalence among those with a history of injecting drug use was 25.1% (95% CI: 0.0%, 66.8%).

Figure 5.3: Prevalence of HCV antibodies by number of medical injections received in the last 6 months.



5.3.5. Multivariable associations

I examined demographic and potential exposures and risk factors in a multivariable model, with odds ratios presented in table 5.2. I found similar results to the univariable analysis: that testing positive for anti-HCV was associated with increasing age up to age 40-49 years [aOR 3.51 (95% CI: 1.50, 6.67)] with the odds decreasing slightly for older age groups. Testing anti-HCV positive was also associated with rural residence [aOR 2.58 (95% CI: 1.36, 4.88) vs urban residence]. Anti-HCV positivity was associated with lower educational attainment [aOR 0.35 (95% CI: 0.16, 0.78) for the highest vs lowest level] and receipt of blood transfusions [aOR 1.34 (95% CI: 1.07, 1.69) per transfusion]. When I stratified the analysis by urban and rural residence (table 5.3), these associations, except educational attainment, persisted among rural residents, while among urban residents, only age remained associated with anti-HCV positivity. I did not find a difference in the prevalence of anti-HCV infection among those who received a blood transfusion before 2002 [6.4% (95% CI: 3.1%, 9.7%)] and those who received one during or after 2002 [4.5% (95% CI: 0.9%, 8.1%)], OR 0.88 (95% CI: 0.34, 2.28).

Table 5.4 shows the multivariable associations stratified by sex. For both males and females higher age was associated with increased odds of HCV infection. Living in a rural setting was associated with a higher odds of anti-HCV positivity for males [aOR 3.39 (95% CI: 1.40, 8.22)] but was only weakly associated among females [aOR 1.96 (95% CI: 0.99, 3.90)]. Similarly, the number of medical injections received in the last 6 months [aOR 1.02 (95% CI: 1.00, 1.03)] and the number of blood transfusions received [aOR 1.37 (95% CI: 1.00, 1.86)] were both associated with increased odds of HCV infection among males but not females [aOR 0.99 (95% CI: 0.96, 1.02) and 1.32 (95% CI: 0.96, 1.81), respectively]. Having the last injection given by a registered nurse or medical practitioner as opposed to a medical doctor was positively associated with HCV among females [aOR 1.97 (95% CI: 1.05, 3.70)] but not males [aOR 1.25 (95% CI: 0.63, 2.46)]. A higher education was associated with a lower odds of HCV infection among females [aOR 0.53 (95% CI 0.34, 0.84) for middle/secondary school education vs none/primary] but not males [aOR 1.11 (95% CI: 0.69, 1.79)]. Having a body piercing was not associated with HCV among females [aOR 0.79 (95% CI: 0.21, 2.99)], nor was shaving at a barber among males [aOR 1.08 (95% CI: 0.64, 1.81)]. Although in a univariable analysis the number of childbirths among females was associated with increased odds of HCV infection [OR 1.23 (95% CI: 1.09, 1.40)], in

the multivariable analysis there was no evidence of such an effect [aOR 0.96 (95% CI: 0.76, 1.20)].

5.3.6. Sensitivity analyses

Results in table 5.2 were similar to those for a sensitivity analysis restricted to individuals aged over 18 years old (table 5.5), and a sensitivity analysis restricted to the two highest prevalence age groups – 40-49 and 50-59 years (table 5.6).

5.3.7. Cumulative exposures

When I examined anti-HCV prevalence by the number of unique potential exposures, compared to persons without these potential exposures, the HCV prevalence increased as the cumulative number of unique exposures increased (figure 5.4). The same analysis revealed that overall 77% of participants had one or more type of potential exposure.

Table 5.2: Weighted unadjusted and mutually adjusted ORs for having HCV antibodies, by participant characteristics and risk factors.

	Total	Odds Ratio (95% Confidence Interval)	
Variables	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**
Age (years)			
5-18	0.7% (0.1%, 1.2%)	0.39 (0.15, 1.01)	0.35 (0.15, 0.79)
19-29	1.7% (0.8%, 2.5%)	1	1
30-39	4.3% (2.9%, 5.7%)	2.64 (1.43, 4.89)	2.45 (1.18, 5.07)
40-49	6.2% (4.4%, 8.0%)	3.91 (2.20, 6.96)	3.51 (1.50, 6.67)
50-59	5.8% (3.9%, 7.7%)	3.66 (2.12, 6.31)	3.13 (1.73, 5.69)
≥60	4.3% (2.7%, 5.8%)	2.65 (1.43, 4.90)	2.01 (1.00, 4.06)
Setting			
Urban	1.6% (1.1%, 2.2%)	1	1
Rural	4.7% (3.8%, 5.7%)	3.01 (2.00, 4.55)	2.58 (1.36, 4.88)
Sex			
Female	3.2% (2.5%, 3.9%)	1	1
Male	4.0% (3.1%, 5.0%)	1.28 (0.95, 1.72)	1.09 (0.34, 3.51)
Household income			
0-20,000 Rupees	3.8% (3.1%, 4.5%)	1	1
>20,000 Rupees	2.5% (1.2%, 3.7%)	0.64 (0.38, 1.09)	0.93 (0.54, 1.58)
Education			
None/Primary	4.7% (3.6%, 5.8%)	1	1
Middle/Secondary	3.3% (2.6%, 4.1%)	0.70 (0.52, 0.95)	0.78 (0.57, 1.06)
Graduate	1.1% (0.3%, 1.8%)	0.21 (0.10, 0.46)	0.35 (0.16, 0.78)
Last injection given by			
Medical Doctor	2.1% (1.2%, 2.9%)	1	1
Registered Nurse/Medical Practitioner	4.4% (3.6%, 5.2%)	2.16 (1.37, 3.42)	1.58 (0.98, 2.55)
Other/Unknown	2.9% (1.7%, 4.0%)	1.38 (0.78, 2.45)	1.28 (0.72, 2.28)
Number injections received last 6 months	NA	1.02 (1.01, 1.03)	1.01 (0.99, 1.02)
Number of times donating blood	NA	0.99 (0.93, 1.05)	0.96 (0.87, 1.05)
Number of blood transfusions received	NA	1.36 (1.10, 1.69)	1.34 (1.07, 1.69)
Number of childbirths	NA	1.08 (0.98, 1.19)	0.93 (0.76, 1.14)
History of surgery			
No	2.9% (2.1%, 4.0%)	1	1
Yes	4.4% (3.2%, 6.1%)	1.54 (1.16, 2.04)	1.16 (0.87, 1.55)
History of dental surgery			
No	2.9% (2.1%, 4.0%)	1	1
Yes	4.6% (3.4%, 6.3%)	1.62 (1.22, 2.14)	1.16 (0.85, 1.57)
Received a permanent tattoo			
No	3.4% (2.8%, 4.1%)	1	1
Yes	5.2% (3.1%, 7.3%)	1.54 (0.97, 2.45)	1.19 (0.78, 1.83)
Received a piercing			
No	3.9% (2.7%, 5.6%)	1	1
Yes	3.3% (2.5%, 4.4%)	0.84 (0.62, 1.13)	0.95 (0.35, 2.54)
Shaves at a barber			
No	3.3% (2.4%, 4.5%)	1	1
Yes	4.9% (3.5%, 6.7%)	1.52 (1.08, 2.13)	1.33 (0.83, 2.11)

Table 5.3: Weighted unadjusted and mutually adjusted ORs for having HCV antibodies, by participant characteristics and risk factors, stratified by urban/rural setting.

	Urban	OR (95% Confidence Interval)		Rural	OR (95% Confidence Interval)	
Variables	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**
Age (years): 5-18	0.5% (0.0%, 1.2%)	0.53 (0.10, 2.92)	0.59 (0.08, 4.27)	0.7% (0.0%, 1.5%)	0.34 (0.11, 1.08)	0.31 (0.13, 0.73)
19-29	1.0% (0.0%, 1.9%)	1	1	2.1% (0.9%, 3.3%)	1	1
30-39	1.0% (0.0%, 2.0%)	1.02 (0.25, 4.12)	1.14 (0.23, 5.58)	6.4% (4.2%, 8.6%)	3.17 (1.58, 6.37)	2.87 (1.24, 6.66)
40-49	4.1% (2.0%, 6.2%)	4.36 (1.41, 13.5)	5.26 (1.48, 18.73)	7.5% (4.9%, 10.1%)	3.78 (1.94, 7.40)	3.12 (1.50, 6.46)
50-59	2.4% (0.8%, 4.1%)	2.55 (0.83, 7.89)	3.45 (0.75, 15.94)	8.2% (5.2%, 11.3%)	4.18 (2.23, 7.82)	3.04 (1.63, 5.70)
≥60	1.2% (0.0%, 2.5%)	1.20 (0.27, 5.44)	1.57 (0.20, 12.14)	5.8% (3.6%, 8.0%)	2.86 (1.43, 5.70)	2.03 (0.95, 4.34)
Sex: Female	1.7% (0.9%, 2.5%)	1	1	4.1% (3.1%, 5.0%)	1	1
Male	1.6% (0.8%, 2.3%)	0.94 (0.49, 1.77)	0.69 (0.09, 5.32)	5.5% (4.1%, 7.0%)	1.38 (0.98, 1.93)	1.20 (0.29, 4.99)
Household income: 0-20,000 Rupees	1.8% (1.1%, 2.6%)	1	1	4.8% (3.8%, 5.7%)	1	1
>20,000 Rupees	1.2% (0.4%, 2.0%)	0.65 (0.29, 1.44)	0.76 (0.26, 2.19)	4.7% (1.7%, 7.7%)	0.99 (0.50, 1.96)	1.02 (0.57, 1.82)
Education: None/Primary	1.7% (0.6%, 2.8%)	1	1	5.9% (4.4%, 7.3%)	1	1
Middle/Secondary	2.0% (1.1%, 2.8%)	1.16 (0.53, 2.56)	1.21 (0.52, 2.80)	4.2% (3.1%, 5.3%)	0.74 (0.55, 0.99)	0.71 (0.50, 1.00)
Graduate	0.8% (0.0%, 1.5%)	0.45 (0.13, 1.50)	0.58 (0.12, 2.77)	1.6% (0.0%, 3.3%)	0.31 (0.09, 1.04)	0.35 (0.13, 0.90)
Last injection given by: Medical Doctor	1.1% (0.3%, 2.0%)	1	1	3.1% (1.6%, 4.6%)	1	1
Registered Nurse/Medical Practitioner	2.3% (1.3%, 3.4%)	2.08 (0.87, 4.99)	1.73 (0.62, 4.84)	5.3% (4.2%, 6.4%)	2.16 (1.28, 3.66)	1.57 (0.91, 2.72)
Other/Unknown	0.9% (0.1%, 1.7%)	0.80 (0.25, 2.52)	0.71 (0.27, 1.82)	4.3% (2.5%, 6.2%)	1.60 (0.71, 3.58)	1.49 (0.75, 2.97)
Number injections received last 6 months	NA	1.03 (0.99, 1.07)	1.01 (0.97, 1.06)	NA	1.01 (1.00, 1.03)	1.00 (0.99, 1.02)
Number of times donating blood	NA	0.99 (0.91, 1.08)	0.97 (0.88, 1.06)	NA	1.01 (0.94, 1.08)	0.96 (0.84, 1.09)
Number of blood transfusions received	NA	1.05 (0.69, 1.60)	1.02 (0.66, 1.58)	NA	1.56 (1.15, 2.10)	1.43 (1.05, 1.96)
Number of childbirths	NA	1.14 (0.92, 1.42)	0.94 (0.60, 1.47)	NA	1.06 (0.95, 1.17)	0.93 (0.73, 1.18)
History of surgery: No	1.4% (0.8%, 2.5%)	1	1	3.8% (2.6%, 5.4%)	1	1
Yes	1.9% (0.9%, 3.9%)	1.36 (0.59, 3.09)	0.98 (0.43, 2.23)	6.1% (4.3%, 8.6%)	1.64 (1.22, 2.20)	1.24 (0.91, 1.69)
History of dental surgery: No	1.5% (0.9%, 2.5%)	1	1	3.6% (2.5%, 5.2%)	1	1
Yes	1.7% (0.8%, 3.7%)	1.12 (0.55, 2.31)	0.83 (0.39, 1.78)	6.7% (4.8%, 9.4%)	1.92 (1.40, 2.64)	1.27 (0.90, 1.80)
Received a permanent tattoo: No	1.6% (1.0%, 2.2%)	1	1	4.5% (3.6%, 5.5%)	1	1
Yes	2.2% (0.1%, 4.3%)	1.42 (0.49, 4.09)	1.40 (0.49, 4.05)	6.9% (3.9%, 10.0%)	1.57 (0.94, 2.63)	1.15 (0.71, 1.87)
Received a piercing: No	1.5% (0.7%, 3.1%)	1	1	5.4% (3.6%, 8.0%)	1	1
Yes	1.7% (1.0%, 3.1%)	1.16 (0.52, 2.58)	1.17 (0.31, 4.43)	4.2% (3.1%, 5.8%)	0.78, (0.56, 1.08)	0.89 (0.26, 3.03)
Shaves at a barber: No	1.4% (0.8%, 2.5%)	1	1	4.3% (3.0%, 6.2%)	1	1
Yes	2.4% (1.2%, 4.7%)	1.70 (0.94, 3.07)	2.05 (0.64, 6.57)	6.5% (4.5%, 9.3%)	1.52 (1.02, 2.26)	1.24 (0.73, 2.10)

Table 5.4: Weighted unadjusted and mutually adjusted ORs for having HCV antibodies, by participant characteristics and risk factors, stratified by sex.

	Male	OR (95% Confidence Interval)		Female	OR (95% Confidence Interval)	
Variables	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**
Age (years): 5-18	0.0% (0.0%, 0.0%)	NA	NA	0.1% (0.1%, 3.0%)	1.12 (0.46, 2.74)	0.75 (0.20, 2.77)
19-29	2.1% (1.0%, 4.4%)	1	1	1.3% (0.1%, 3.2%)	1	1
30-39	7.0% (4.3%, 11.2%)	3.44 (1.44, 8.22)	3.76 (1.65, 8.59)	2.3% (1.4%, 3.9%)	1.88 (0.61, 5.74)	1.45 (0.53, 3.98)
40-49	6.5% (3.8%, 10.8%)	3.15 (1.34, 7.43)	3.38 (1.47, 7.74)	6.0% (4.0%, 8.9%)	5.04 (1.99, 12.77)	3.22 (1.36, 7.64)
50-59	7.3% (4.6%, 11.3%)	3.58 (1.58, 8.12)	3.72 (1.61, 8.63)	4.7% (2.9%, 7.4%)	3.83 (1.55, 9.50)	2.25 (1.01, 5.00)
≥60	4.4% (2.5% (7.5%)	2.08 (0.79, 5.47)	1.95 (0.77, 4.94)	4.2% (2.4%, 7.4%)	3.47 (1.40, 8.58)	1.77 (0.85, 3.71)
Setting: Urban	1.6% (0.1%, 3.1%)	1	1	1.7% (0.9%, 3.0%)	1	1
Rural	5.5% (3.8%, 8.0%)	3.67 (1.67, 8.08)	3.39 (1.40, 8.22)	4.1% (2.9%, 5.7%)	2.50 (1.24, 5.03)	1.96 (0.99, 3.90)
Household income: 0-20,000 Rupees	4.4% (3.2%, 6.0%)	1	1	3.4% (2.4%, 4.6%)	1	1
>20,000 Rupees	2.6% (1.2%, 5.6%)	0.58 (0.28, 1.22)	0.82 (0.36, 1.86)	2.4% (1.3%, 4.4%)	0.71 (0.35, 1.40)	1.06 (0.55, 2.03)
Education: None/Primary	4.3% (2.8%, 6.5%)	1	1	5.0% (3.6%, 7.0%)	1	1
Middle/Secondary	4.4% (3.1%, 6.3%)	1.03 (0.68, 1.57)	1.11 (0.69, 1.79)	2.2% (1.5%, 3.4%)	0.43 (0.28, 0.67)	0.53 (0.34, 0.84)
Graduate	1.6% (0.6%, 4.6%)	0.37 (0.12, 1.13)	0.67 (0.20, 2.20)	0.6% (0.2%, 1.9%)	0.11 (0.03, 0.40)	0.19 (0.05, 0.73)
Last injection given by: Medical Doctor	2.8% (1.6%, 4.8%)	1	1	1.6% (0.9%, 2.8%)	1	1
Registered Nurse/Medical Practitioner	4.7% (3.3%, 6.6%)	1.72 (0.94, 3.17)	1.25 (0.63, 2.46)	4.1% (3.0%, 5.6%)	2.69 (1.43, 5.08)	1.97 (1.05, 3.70)
Other/Unknown	3.3% (1.6%, 6.7%)	1.21 (0.58, 2.52)	1.14 (0.53, 2.43)	2.4% (1.3%, 4.6%)	1.56 (0.61, 4.01)	1.37 (0.54, 3.47)
Number injections received last 6 months	NA	1.03 (1.01, 1.04)	1.02 (1.00, 1.03)	NA	1.01 (0.99, 1.03)	0.99 (0.96, 1.02)
Number of times donating blood	NA	0.98 (0.91, 1.05)	0.94 (0.83, 1.06)	NA	0.56 (0.16, 2.03)	0.69 (0.19, 2.55)
Number of blood transfusions received	NA	1.28 (0.98, 1.68)	1.37 (1.00, 1.86)	NA	1.47 (1.07, 2.01)	1.32 (0.96, 1.81)
Number of childbirths	NA	NA	NA	NA	1.23 (1.09, 1.40)	0.96 (0.76, 1.20)
History of surgery: No	3.5% (2.4%, 4.9%)	1	1	2.4% (1.6%, 3.5%)	1	1
Yes	5.1% (3.3%, 7.8%)	1.49 (0.95, 2.35)	1.19 (0.74, 1.92)	4.0% (3.0%, 5.5%)	1.74 (1.21, 2.49)	1.25 (0.88, 1.77)
History of dental surgery: No	3.4% (2.3%, 5.0%)	1	1	2.4% (1.6%, 3.5%)	1	1
Yes	5.1% (3.4%, 7.6%)	1.50 (0.96, 2.35)	1.08 (0.68, 1.71)	4.3% (3.0%, 6.0%)	1.82 (1.22, 2.72)	1.23 (0.80, 1.89)
Received a permanent tattoo: No	3.7% (2.5%, 5.5%)	1	1	3.2% (2.4%, 4.3%)	1	1
Yes	6.0% (4.1%, 8.6%)	1.66 (0.99, 2.77)	1.32 (0.77, 2.27)	1.6% (0.2%, 10.8%)	0.48 (0.07, 3.16)	0.39 (0.04, 3.47)
Received a piercing: No	4.0% (2.8%, 5.7%)	1	1	2.2% (0.6%, 8.3%)	1	1
Yes	4.5% (2.2%, 9.1%)	1.14 (0.50, 2.56)	1.14 (0.50, 2.58)	3.2% (2.4%, 4.3%)	1.49 (0.41, 5.36)	0.79 (0.21, 2.99)
Shaves at a barber: No	3.4% (2.1%, 5.4%)	1	1	3.2% (2.4%, 4.3%)	1	1
Yes	4.9% (3.5%, 6.7%)	1.45 (0.90, 2.32)	1.08 (0.64, 1.81)	NA	NA	NA

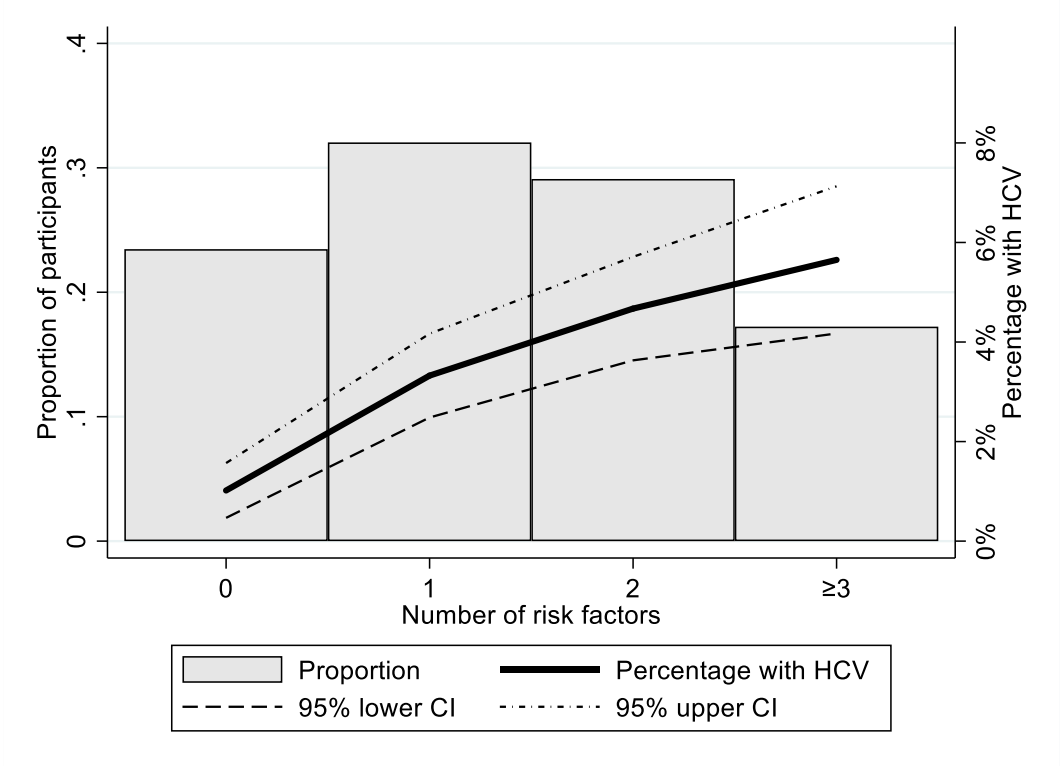
Table 5.5: Weighted unadjusted and mutually adjusted ORs for having HCV antibodies, by participant characteristics and risk factors for adults aged over 18 years old.

	Total	Odds Ratio (95% Confidence Interval)	
Variables	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**
Total	4.3% (3.6%, 5.1%)		
Age (years)			
19-29	1.7% (0.8%, 2.5%)	1	1
30-39	4.3% (2.9%, 5.7%)	2.64 (1.43, 4.89)	2.39 (1.15, 4.97)
40-49	6.2% (4.4%, 8.0%)	3.91 (2.20, 6.96)	3.31 (1.72, 6.37)
50-59	5.8% (3.9%, 7.7%)	3.66 (2.12, 6.31)	2.86 (1.52, 5.39)
≥60	4.3% (2.7%, 5.8%)	2.65 (1.43, 4.90)	1.77 (0.86, 3.63)
Setting			
Urban	1.9% (1.1%, 3.2%)	1	1
Rural	5.8% (4.2%, 7.9%)	3.20 (2.09, 4.89)	2.64 (1.37, 5.11)
Sex			
Female	3.6% (2.8%, 4.3%)	1	1
Male	5.2% (4.0%, 6.5%)	1.50 (1.10, 2.04)	1.79 (0.55, 5.83)
Household income			
0-20,000 Rupees	4.7% (3.8%, 5.5%)	1	1
>20,000 Rupees	2.8% (1.3%, 4.2%)	0.58 (0.34, 1.00)	0.93 (0.53, 1.64)
Education			
None/Primary	6.1% (4.6%, 7.5%)	1	1
Middle/Secondary	4.1% (3.1%, 5.0%)	0.66 (0.48, 0.90)	0.75 (0.54, 1.06)
Graduate	1.1% (0.3%, 1.8%)	0.17 (0.08, 0.36)	0.37 (0.16, 0.82)
Last injection given by			
Medical Doctor	2.3% (1.2%, 3.3%)	1	1
Registered Nurse/Medical Practitioner	5.3% (4.3%, 6.3%)	2.43 (1.48, 3.97)	1.76 (1.10, 2.82)
Other/Unknown	3.6% (2.2%, 5.1%)	1.64 (0.90, 2.99)	1.49 (0.80, 2.78)
Number injections received last 6 months	NA	1.02 (1.00, 1.03)	1.01 (0.99, 1.02)
Number of times donating blood	NA	0.97 (0.89, 1.04)	0.95 (0.86, 1.05)
Number of blood transfusions received	NA	1.32 (1.07, 1.63)	1.35 (1.07, 1.70)
Number of childbirths	NA	0.99 (0.89, 1.10)	1.00 (0.83, 1.22)
History of surgery			
No	3.9% (2.8%, 5.4%)	1	1
Yes	4.7% (3.4%, 6.5%)	1.22 (0.90, 1.67)	1.19 (0.88, 1.62)
History of dental surgery			
No	3.9% (2.9%, 5.3%)	1	1
Yes	4.8% (3.5%, 6.6%)	1.24 (0.93, 1.64)	1.16 (0.85, 1.57)
Received a permanent tattoo			
No	4.2% (3.4%, 5.0%)	1	1
Yes	5.5% (3.3%, 7.7%)	1.35 (0.85, 2.14)	1.13 (0.73, 1.76)
Received a piercing			
No	5.3% (3.7%, 7.5%)	1	1
Yes	3.6% (2.7%, 4.8%)	0.68 (0.49, 0.94)	1.06 (0.39, 2.88)
Shaves at a barber			
No	4.1% (3.0%, 5.5%)	1	1
Yes	5.1% (3.7%, 7.1%)	1.27 (0.91, 1.78)	1.19 (0.73, 1.93)

Table 5.6: Weighted unadjusted and mutually adjusted ORs for having HCV antibodies, by participant characteristics and risk factors overall for adults aged 40-59 years old.

Variables	Total Anti-HCV % (95% CI)	Odds Ratio (95% Confidence Interval) Unadjusted OR	 Adjusted OR
Total	6.0% (4.3%, 8.3%)		
Setting			
Urban	3.3% (1.7%, 6.4%)	1	1
Rural	7.8% (5.4%, 11.2%)	2.48 (1.11, 5.53)	1.86 (0.77, 4.52)
Sex			
Female	5.4% (3.7%, 7.8%)	1	1
Male	6.9% (4.5%, 10.4%)	1.28 (0.80, 2.05)	2.37 (0.36, 15.84)
Household income			
0-20,000 Rupees	6.3% (4.6%, 8.8%)	1	1
>20,000 Rupees	4.8% (2.6%, 8.8%)	0.74 (0.41, 1.34)	1.25 (0.64, 2.45)
Education			
None/Primary	8.6% (6.0%, 12.3%)	1	1
Middle/Secondary	4.7% (3.0%, 7.6%)	0.53 (0.31, 0.90)	0.60 (0.34, 1.06)
Graduate	1.6% (0.5%, 4.9%)	0.17 (0.05, 0.56)	0.26 (0.07, 0.89)
Last injection given by			
Medical Doctor	2.9% (1.6%, 5.5%)	1	1
Registered Nurse/Medical Practitioner	7.9% (5.6%, 11.1%)	2.83 (1.53, 5.22)	2.19 (1.13, 4.21)
Other/Unknown	4.1% (2.4%, 6.8%)	1.40 (0.65, 3.00)	1.34 (0.63, 2.86)
Number injections received last 6 months	NA	1.01 (0.99, 1.03)	1.00 (0.98, 1.02)
Number of times donating blood	NA	0.91 (0.76, 1.08)	0.91 (0.75, 1.12)
Number of blood transfusions received	NA	1.35 (1.01, 1.81)	1.46 (1.12, 1.90)
Number of childbirths	NA	0.99 (0.86, 1.14)	1.08 (0.85, 1.36)
History of surgery			
No	5.1% (3.5%, 7.3%)	1	1
Yes	6.8% (4.6%, 9.9%)	1.37 (0.91, 2.06)	1.45 (0.95, 2.21)
History of dental surgery			
No	6.9% (4.8%, 9.9%)	1	1
Yes	5.4% (3.6%, 8.0%)	0.77 (0.51, 1.15)	0.84 (0.56, 1.25)
Received a permanent tattoo			
No	5.9% (4.3%, 8.1%)	1	1
Yes	7.6% (3.7%, 14.9%)	1.30 (0.66, 2.56)	0.98 (0.44, 2.19)
Received a piercing			
No	6.8% (4.4%, 10.3%)	1	1
Yes	5.5% (3.8%, 7.8%)	0.80 (0.51, 1.27)	1.18 (0.25, 5.53)
Shaves at a barber			
No	5.7% (4.0%, 8.2%)	1	1
Yes	7.3% (4.4%, 12.0%)	1.30 (0.72, 2.34)	1.13 (0.55, 2.31)

Figure 5.4: Prevalence of HCV antibodies by unique potential exposures†.



† Whether they had a history of surgery, whether they had a history of dental surgery, whether they shave at a barber, whether they had ever received a blood transfusion, and whether in the last 6 months they had received a medical injection.

5.4. Discussion

5.4.1. Main findings

In this serosurvey in Punjab, India, there was an overall weighted prevalence of anti-HCV of 3.6% and HCV RNA of 2.6%. I found that males, persons aged 40-59, and persons living in rural areas had the greatest odds of being infected with HCV. Additionally, HCV infection was more common among those who lacked education, had received a blood transfusion, and had their last injection given by a nurse or other medical practitioner as compared to a medical doctor. Through multivariable analysis, I found no increased likelihood of being anti-HCV positive with increases in the reported number of participants' medical injections received by participants in the last 6 months.

Due to the increasing prevalence with age, it may be tempting to consider that transmission risk has decreased over time and younger people are at lower risk. However, the youngest age groups studied, 5-18- and 19-29-year olds, had HCV seropositive rates of over 1% and 2% respectively, suggesting that transmission risk persists in Punjab. In fact, a rise in prevalence of injection drug use in Punjab has been described among teens and the youth population(261) and may present an emerging risk for HCV infection in similarly aged populations in the years to come. Very few disclosed injecting drug use in the serosurvey, which may reflect social desirability bias on the part of participants – the role of injecting drug use to HCV transmission is examined in chapter 7.

Residence in a rural versus urban area was determined to be an effect modifier in this analysis. Individuals in rural areas of Punjab had 2.5 times the odds of being anti-HCV positive as those in urban settings after adjusting for covariates, a result comparable to another study from North India(226). Upon stratification, I found that age, education, and blood transfusions were associated with HCV among participants in rural areas, whereas in urban areas the only association was with age. Poverty, defined by a household income <20,000 rupees, was not associated with infection in this analysis. There is a paucity of trained healthcare professionals in rural areas of Punjab, so healthcare in those regions is often delivered by unqualified practitioners who may adopt unsafe injection practices(336), possibly contributing to the elevated prevalence of HCV among rural residents in Punjab that I identified in comparison with urban areas.

The finding that blood transfusions were associated with HCV highlights the need for improved blood safety practices in Punjab. Mandatory testing for HCV was implemented in blood banks in India in 2002(303). However, participants in the serosurvey who received their first transfusion in 2002 or later were no less likely to be anti-HCV positive than those who received transfusions before mandatory testing began. Despite the existence of state-wide blood safety guidelines, an association between receipt of a blood transfusion and having HCV infection persisted in this serosurvey, regardless of when the blood transfusions were received, and may suggest a persistent mode of HCV transmission in Punjab. These findings underscore the need for greater enforcement and monitoring of blood banks to ensure proper testing procedures are followed to prevent transmission in these settings.

5.4.2. Strengths and limitations

This analysis is subject to several limitations. First, it was not possible to independently verify any of the responses on the questionnaire. Also, the number of non-responders could not be determined, although it was reported from the field that interest was very high and 98% of households participated. False positive anti-HCV among those that tested negative for RNA cannot be ruled out. As with any cross-sectional study that examines a chronic condition, it is challenging to attribute risk due to lack of temporality, as the HCV infection could have occurred at any time during the lifetime of the study subjects. A global analysis found a large reduction in the re-use of medical syringes, and the viruses that arise from them, in each region from 2000 to 2010(282, 283). This serosurvey asks about the use of medical injections in the last 6 months, so many infections due to HCV could have occurred in the time period before this. As discussed in chapter 4, associations in cross-sectional studies can be particularly challenging to discern with highly prevalent behaviours, such as medical injections in this setting.

The sampling method of this study, which included multiple participants from a single household, could lead to potential selection bias. Persons living together are more likely to exhibit similar behaviours and could lead to disproportionate risks in the sample that may not be representative of the greater population. Additionally, the sampling method of the serosurvey was not designed to produce precise per-region prevalence estimates; there was

a preponderance of people surveyed from rural areas in districts that were found to have a high prevalence of HCV. These results should be interpreted with caution, as this could lead to overestimation of the prevalence in these areas. The face-to-face nature of the questionnaire creates the potential for social desirability bias. Injection drug use is a significant risk factor for HCV, but self-report of this behaviour was extremely low (0.09%) among participants in this serosurvey despite reports of worrisome trends of increased injection drug use in the state(326, 359). The number of persons associated with some of the exposures and risk factors, notably dialysis (n=26) and injection drugs (n=5), was small, making associations of these risk factors with HCV seropositivity difficult to determine. Thus, an important risk behaviour may be substantially underrepresented in this analysis.

5.4.3. Comparison with other literature

The association of HCV with age and rural residence has been observed in previous studies from Punjab(335). Studies from other countries have also identified a particular age or birth cohort with a high prevalence of HCV compared to others, consistent with the analyses in Pakistan in chapter 4(165, 351). This cohort effect is demonstrated by persons born between 1945 and 1965, so called "Baby Boomers" in the United States(266, 338). In the United States, the higher HCV prevalence among Baby Boomers has been attributed largely to injection drug use during their youth, the lack of an HCV screening test for blood and blood products prior to 1990, and to the effect of the HIV epidemic, recognised during the 1980s(266, 338). The reason behind the greater HCV prevalence in Punjab among those aged 40-59 is unclear; perhaps transmission rates were higher in the past and infected individuals aged ≥60 years have died more quickly. My sensitivity analysis examining associations among this age group found similar results to that the analysis containing all age groups.

Previous studies have also found inadequate infection control practices among healthcare workers in India(87, 253), however, the number of medical injections was not associated with HCV after adjusting for covariates in this study. It is important to note that in a cross-sectional study, to identify associations with medical practices is challenging. However, we found an increased likelihood of being anti-HCV positive among those who received their last injection from someone other than a medical doctor. As discussed in chapter 4, Kot Imrana in Punjab, Pakistan, suffered an outbreak of bloodborne viruses in 2018/2019,

particularly HIV(386); it is thought that this outbreak was initially sparked by the re-use of medical injections by untrained medical practitioners(386). A 2002 study in Punjab (India) found that a considerable percentage of physicians with knowledge of parenteral HCV transmission risk nevertheless reused needles and syringes with their patients(343). Furthermore, in Punjab and throughout India, treatment with injectable medicine is perceived to be the treatment that ensures rapid therapeutic relief(297). This belief has been inculcated over many years by physicians themselves, and there are financial incentives to deliver treatment through a "procedure", such as an injection(297). Although increased availability of disposable syringes helps temper these risks, healthcare workers throughout Punjab could benefit from further training on safe injection practices to prevent the spread of HCV and other diseases.

Unlike in this chapter focusing on Punjab, India, in chapter 4 I found an association between the number of medical injections received and HCV infection in Pakistan. This could be because the use of unsafe medical injections is less prevalent in Punjab. In Pakistan there was evidence of a positive association between childbirth and HCV infection, however, this was not evident in Punjab perhaps due to different practices surrounding childbirths. Both this chapter and chapter 4 found that having received blood transfusions was associated with HCV prevalence. Neither analysis found a history of surgery or of dental surgery were associated with HCV infection, whilst both chapters identified socio-economic markers associated with HCV infection: illiteracy and employment type in Pakistan, and education in Punjab. However, whilst community risk factors (body-piercings, tattoos, shaving at the barbers) were associated with HCV in Pakistan, in Punjab none were associated with HCV prevalence, which is possibly due to different equipment sterilisation practices in each setting.

5.4.4. Implications

The prevalence of chronic HCV infection found in this serosurvey was slightly less than was determined by a 2012 study in the region(344), but in a population of roughly 28 million, still translates to nearly three quarters of a million people chronically infected in the state of Punjab alone. Future screening efforts need to address this burden of disease to identify infected individuals and link them to care and treatment. Population serosurveys, such as

the study in Punjab presented here, can address key information gaps and inform policy makers in efforts to alleviate the public health burden of HCV infection across afflicted regions worldwide(387). As with chapter 4 in Pakistan, the results of this study can be used to target screening and linkage to care efforts in Punjab state, to ensure the highest yield of HCV infected individuals, whilst minimising costs. Screening efforts in Punjab should target rural districts, persons aged 30 and older, and those with history of receiving blood transfusions. India's expenditure on health care as a percentage of its gross domestic product (1.3% in 2015-2016) is among the lowest in the world, and the country has no system to monitor patients(5). Nationwide surveillance of hepatitis is also lacking in the country and focuses primarily on hepatitis A and E(203). Testing for incident HCV and HBV cases is only supported by the country's national Integrated Disease Surveillance Programme (IDSP) in outbreak situations(203). Fortunately, treatment costs for HCV infection in India have decreased significantly with the introduction of direct acting antiviral drugs in 2015, which have proven to be highly effective(345). In 2016, Punjab became the first state in India to make the commitment to treat HCV patients free of charge(80, 361). Through July 2017, over 32,000 patients have been treated through the program(361), representing an important step in control of the disease. With treatment options becoming more effective, affordable, and available to patients, there is hope that Punjab could be reaching a turning point to mitigate the burden of HCV. However, access to treatment alone cannot end the epidemic of HCV globally or in Punjab. Indeed, as DAA access has expanded in other settings, such as Australia, after the first couple years the initial very high numbers of people starting treatment have declined(205). This has been called a warehousing effect as whilst waiting for treatment to become available, the number of people that know they are HCV-infected builds up – the "warehousing"(205). This leads to high initial numbers that start treatment as those already diagnosed are able to access treatment, but these numbers reduce when there are less diagnosed people to treat(205). Therefore, more information on screening strategies is required to enable high rates of diagnosis so the high numbers of people starting HCV treatment can continue. This will be influenced by analysing data from serosurveys such as in this chapter.

Additionally, when designing a treatment programme such as that in Punjab, it is important to understand how different subgroups of infected individuals contribute to the HCV epidemic in that setting. To this end, in chapter 7 I investigate the contribution of injecting drug use to HCV transmission for 88 countries around the world. When designing these

programmes, it is also important to understand the preventative effect of treatment on further transmission. In chapter 8 I estimate the infections averted per each DAA treatment given for different subgroups of infected individuals.

CHAPTER 6. MODELLING THE GLOBAL HEPATITIS C VIRUS EPIDEMIC

The work in this chapter was done in collaboration with Hannah Fraser, Aaron G Lim, Amy Peacock, Samantha Colledge, Josephine G Walker, Janni Leung, Jason Grebely, Sarah Larney, Natasha K Martin, Matthew Hickman, Louisa Degenhardt, Margaret T May, and Peter Vickerman. This chapter forms the basis of the methods used in chapters 8 and 9.

6.1. Introduction

The model presented in this chapter is of country-level hepatitis C virus (HCV) transmission, incorporating HCV transmission among people who inject drugs (PWID) and the general population (non-PWID). The HCV transmission model is stratified into nine disease and treatment strata (figure 6.1), with each of these then stratified by seven age and injecting status strata (figure 6.2). This makes up 63 model compartments in total. Chapter 7 uses the model presented in this chapter to investigate the contribution of injection drug use (IDU) to HCV transmission globally, whilst chapter 8 uses this model to estimate the impact of treatment as prevention for different infected population subgroups.

These dynamic, deterministic HCV transmission models simulating country-level HCV epidemics among the general population and PWID, incorporate age distributions (0–14, 15–34, and ≥35–year olds), IDU, population growth, and HCV progression.

6.2. Model structure

6.2.1. Age and injecting model structure

Individuals transition through age and injecting model strata as shown in figure 6.1. Most individuals enter the model at a rate R(t) into the 0-14-year-old compartment as susceptible to infection (except those that enter as infected via vertical transmission). The rate R(t) is set to balance all non-HCV-related and non-drug related deaths (DR_1, DR_2 and DR_3 for those aged 0-14, 15-34, and ≥35 years, respectively), while also allowing for population growth at a

specified rate. Other than becoming infected, young individuals can age (at rate a) to become young adults that do not inject drugs – referred to in the diagram as non-PWID - (aged 15-34 years), from which they can age (at rate b) to becoming older adults that do not inject drugs (aged ≥35 years). Adults that do not inject drugs (aged 15-34 years) can also transition (at rate φ) to become PWID (current injectors). I assume that adults aged ≥35 do not start injecting drugs. However, adults aged ≥35 can be current injectors by ageing from the currently injecting aged 15-34 category; ageing at rate b. This assumption was based on data from a recent global meta-analysis that identified the average age of onset of injecting drug use across studies to be 22 years old, with the minimum average age of onset being 13 and maximum 39(77). PWID inject for an average duration until they transition (at rate v) to become people who used to inject drugs (referred to in the diagram as ex-PWID). Young adults (age 15-34 years) that are PWID or used to inject drugs age to their respective older adult (aged ≥35 years) classes just as young adults that do not inject drugs do. All individuals are subject to age category dependent death rates (DR_1, DR_2, DR_3, for those aged 0-14, 15-34, and ≥35 years, respectively), with PWID also being subject to an additional drug-related death rate (μ).

6.2.2. Disease modelling structure

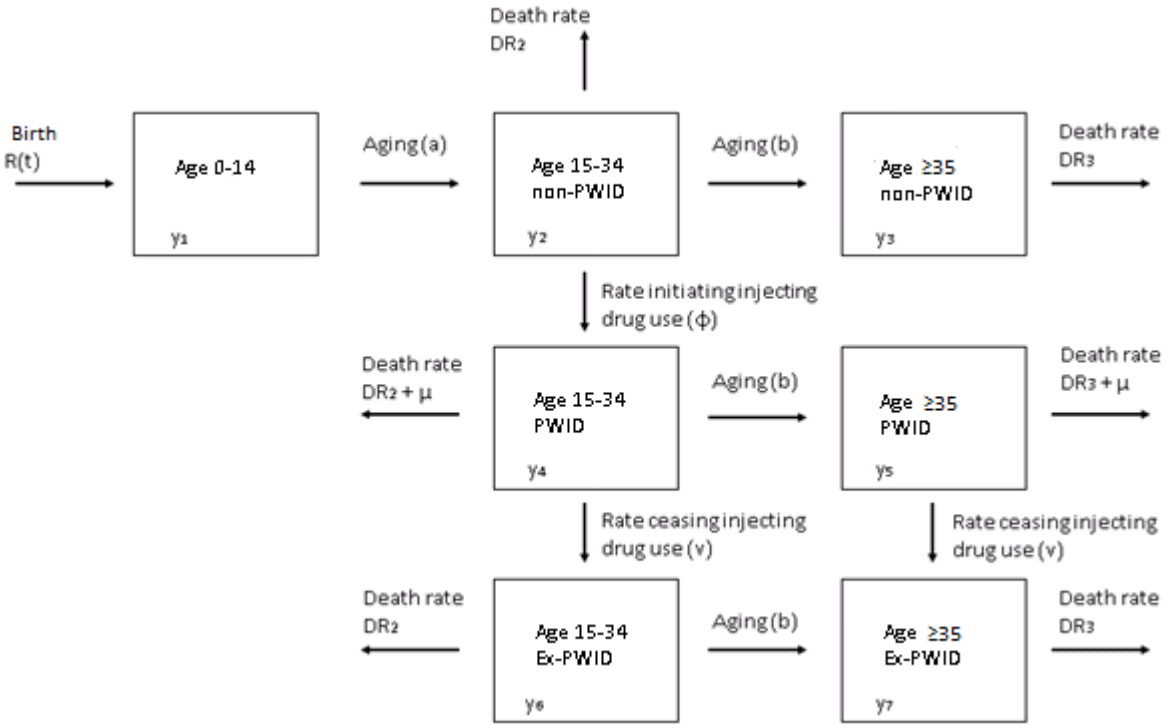
Within the disease state model component, most individuals enter as susceptible individuals (S), from which they can then become infected and transition to the chronically infected state (I) at a per capita transmission rate, $(1-\delta)P$, for the general population (not people who inject drugs), which is increased for PWID to $(1-\delta)(P+\pi)$. P is the force of infection that acts on the whole population, π is the additional force of infection that acts on PWID, and δ is the proportion of new infections that spontaneously clear their infection and so do not progress to chronic infection. Individuals who spontaneously clear infection remain susceptible to re-infection (assuming no immunity after clearance as previous modelling has shown it has little effect on model projections(384)). A certain number of individuals, V(t), which is time varying, enter the model chronically infected due to vertical transmission, this is described in section 6.8.

Once they are chronically infected, individuals progress through different infection and treatment states. Chronically infected individuals progress to the cirrhotic infected state (CI)

at rate γ. Individuals that are cirrhotic infected (CI) can then progress to the decompensated cirrhosis infected state (DI) at rate χ. Individuals in each of these infected groups (chronic [I], cirrhotic [CI], and decompensated [DI]) can receive HCV treatment (and move to the treatment [T], cirrhotic treatment [CT], or decompensated treatment groups [DT], respectively) at a per capita rate, denoted λ. If treatment is successful, individuals achieve a sustained viral response (SVR – effective cure) at a rate $\alpha\omega$, where α is the proportion of people that achieve SVR following treatment, and $1/\omega$ is the length of treatment. Individuals achieving SVR transition from the treatment to their respective susceptible disease stage (susceptible [S], cirrhotic susceptible [CS], or decompensated susceptible groups [DS], depending on their disease stage when they were treated). However, some individuals that receive treatment fail to achieve SVR and move back to their prior infection disease stage at rate $(1-\alpha)\omega$, either chronic (I), cirrhotic (CI), or decompensated infected (DI) groups. We assume disease progression ceases for cured individuals whose HCV infection had not progressed to cirrhosis or later(61), while those with cirrhosis who are cured experience further disease progression at a slower rate (rate ε – slower than χ) than those not achieving SVR or who are infected. There is a further additional liver-related mortality rate, μ_4, for those in the decompensated infected (DI), decompensated treatment (DT), and decompensated susceptible groups (DS). Those in the susceptible, cirrhotic susceptible (CS) and decompensated susceptible groups (DS) can be re-infected at the same rate as for primary infection, but depending on their injecting drug use (IDU) status, and move to the chronically infected (I), cirrhotic infected (CI) and decompensated infected (DI) groups, respectively.

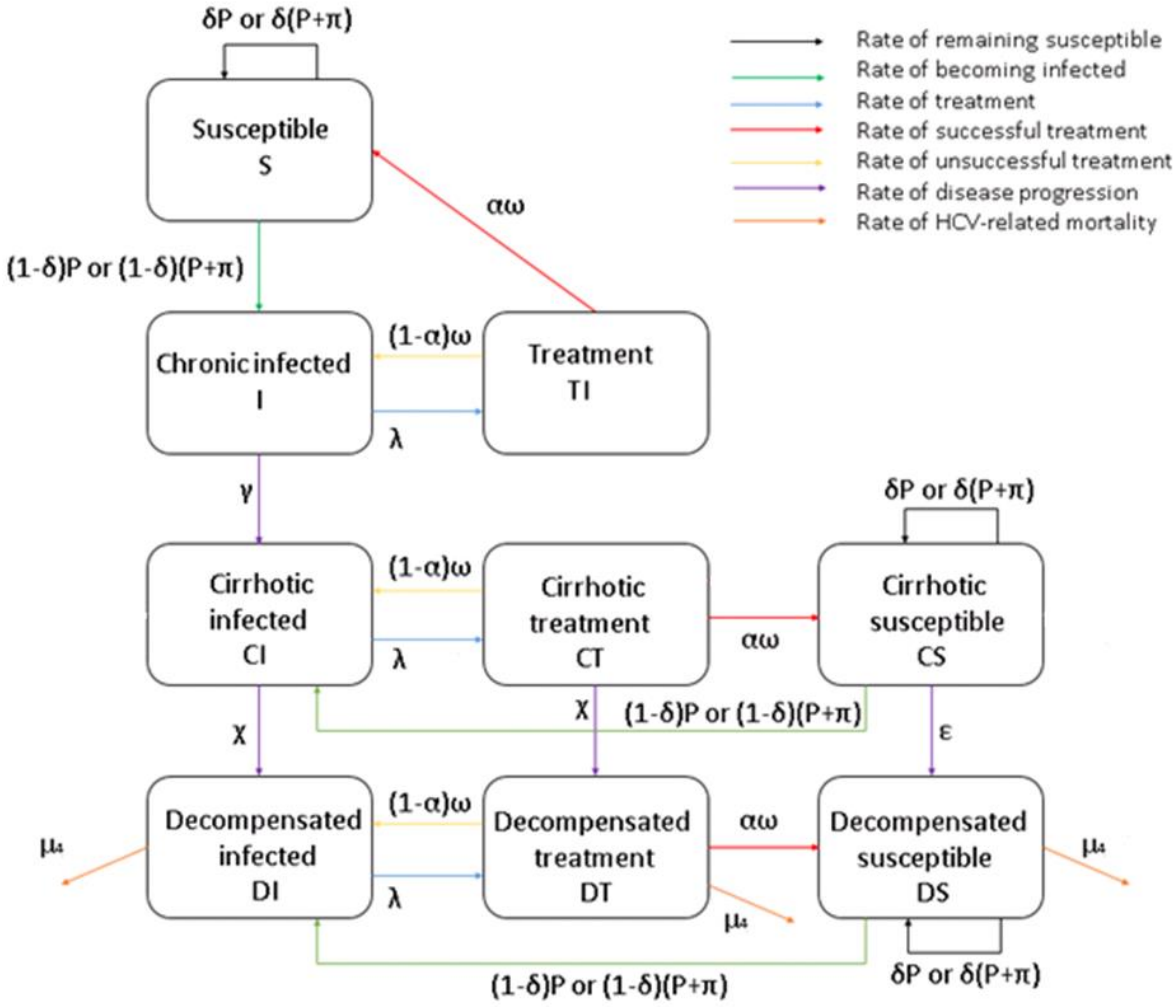
Of note, I assume no transient increase in transmission risk during the acute phase of infection because viral load data suggests no evidence for a peak in HCV viremia during acute infection (except for those that subsequently clear their infection). Therefore, early viral load levels should not affect transmission and so have not been included within the model. Please see "Patterns of Hepatitis C Virus RNA Levels during Acute Infection: The InC3 Study" by Hajarizadeh et al. for more information(136).

Figure 6.1: Schematic of how people move through the seven age and injecting stage groups of the model*.



* PWID denotes people who inject drugs, Ex-PWID denotes those individuals that used to inject drugs, and non-PWID are people that have never injected drugs.

Figure 6.2: Schematic of how people move through the HCV stages of the model*.



* Demographics other than disease related mortality are not shown for clarity.

6.3. Model parameterisation

Country-specific data from recent systematic reviews, particularly Blach et al.(40) and Degenhardt et al.(77), and United Nations (UN) datasets were used to parameterise and calibrate the model, including data on the prevalence of HCV among PWID and the general population, estimates for the population percentage of PWID, and data on population growth rates and age distributions. Table 6.1 gives details on the sources of the data used, whilst table 6.2 gives information on the model parameters, and table 6.3 provides details of parameters that vary by region. Section 6.13 gives information about country-level inputs. The study by Degenhardt et al., from which most estimates of injecting population sizes were taken, states that they preferentially selected size and HCV prevalence estimates that defined current injectors as individuals that have injected drugs in the previous 12 months. However, other estimates using alternative definitions (eg. injecting in the last 6 months) were still included in the review in the absence of the preferred definition. For country-level HCV prevalence estimates, HCV antibody prevalence was taken from the reviews, and was adjusted using region-specific viraemic rates(252) to estimate the prevalence of chronic infection in the survey year – these region-specific viraemic rates do not account for HIV prevalence. Historical treatment numbers were taken from various sources, which are described in section 6.15. All key parameters had uncertainty associated with them, with bounds generally obtained directly from studies. Where bounds were unavailable for prevalence inputs, ±33% uncertainty bounds were applied, which equates to the median level of uncertainty for those parameters that did have bounds - this was to avoid ascribing too much certainty to those estimates with no uncertainty bounds.

Table 6.1: Global model data source summary.

Data	Source
Population sizes and growth rate	United Nations(380)
Age distributions	United Nations(380)
Fertility rates	United Nations(380)
Age-group specific mortality rates	United Nations(380)
Proportion of adults (aged ≥15) that are PWID	Degenhardt et al.(77) and other reviews where necessary, see table 6.8
HCV antibody prevalence among PWID	Degenhardt et al.(77) and other reviews where necessary, see table 6.8
HCV antibody prevalence among the general population*	Blach et al.(40) and other reviews where necessary, see table 6.8
Region-specific viraemic rates amongst sero-positive individuals to estimate chronic infection	Petruziello et al.(285)
Duration of injecting**	Degenhardt et al.(77)
Injecting drug use by gender†	Degenhardt et al.(77)
HIV prevalence among PWID†	Degenhardt et al.(77)
HIV prevalences for women aged 15-24***†	World Bank(365)
Historical treatment numbers	Various, see table 6.10

* Only USA, Egypt, and France have two "robust surveys"(40) (large, national surveys with very similar methodology), with these data being used to model their HCV epidemic dynamics.

** Taken from data on the current duration of injecting, with wide uncertainty bounds being applied (-50%, +100%) to account for uncertainty in how this parameter relates to total duration of injecting.

*** Used to proxy HIV prevalence among women of childbearing age, assumed to be 15-34 years old in my model.

†Included for use in the vertical transmission calculations.

Table 6.2: Model parameters with sampled ranges*.

Parameter	Parameter description	Point value and sampled range	Reference
a	The rate of aging from 0-14 to 15-34	1/15	
b	The rate of aging from 15-34 to ≥35	1/20	
δ	Proportion of individuals spontaneously clearing infection	Region specific (the percentage not advancing to viraemic infection)	Petruziello 2016(285)
γ	The rate of progressing from chronic infection to cirrhosis	0.037 (0.025-0.052); Triangular distribution	Shepherd 2007(328)
χ	The rate of progressing from compensated cirrhosis to decompensated cirrhosis if infected (or on treatment)	0.0453 (0.0363-0.0566); Triangular distribution	Hallager 2017(140)
ε	The rate of progressing from cirrhosis to the decompensated cirrhosis if cured and susceptible	0.01 (0.006-0.0165); Triangular distribution	Hallager 2017(140)
μ_4	Additional death rate for an individual with decompensated cirrhosis	0.13 [Beta distribution: alpha = 14.6, beta = 360.2]	Greive 2006 (129); Shepherd 2007(328); Wright 2003(411)
φ	The initiation rate of becoming a person who currently injects drugs	Fitted to the proportion of adults that are PWID in data from systematic reviews	
v	The rate of ceasing injecting drugs	Sampled from a uniform distribution between region specific bounds	Degenhardt 2017(77)
μ	Additional mortality rate for people who currently inject drugs	High-income countries: 0.0217 (0.0192, 0.0247); Triangular distribution Low and middle-income countries: 0.0353 (0.0281, 0.0424); Triangular distribution	Mathers 2013(246)

Parameter	Parameter description	Point value and sampled range	Reference
λ	Treatment rate	Country-specific and varying with time. Treatment numbers in 2017 (when the data ends) are carried forward, apart from in 2018 when an extra 50 infections are treated in specific groups for the intervention scenarios in chapter 8. If the number of possible annual treatments exceeds the number infected, then a treatment rate of 0.95 is used	See historical treatment numbers section
$1/\omega$	Duration of treatment	Until 2010: 48 weeks for Pegylated interferon. From 2011-2014: 24 weeks due to 1st wave DAAs. From 2015 onwards: 12 weeks due to 2nd wave DAAs	Palumbo 2011 (277); Brouard 2017(48); WHO 2016(400)
α	Proportion achieving sustained virological response with HCV treatments	Until 2010: Uniform between 0.4-0.5 for Pegylated interferon. From 2011-2014: 0.65-0.75. From 2015 onwards: Uniform between 0.9-0.99 due to 2nd wave DAAs	Palumbo 2011(277); Brouard 2017(48) Hezode 2017(155)
q_1	Chance of vertical transmission of HCV RNA per birth among women with HCV RNA that are HIV negative	0.058 (0.042, 0.078); Triangular distribution	Benova 2014(35)
q_2	Chance of vertical transmission of HCV RNA per birth among women with HCV RNA that are HIV positive	0.108 (0.076, 0.152); Triangular distribution	Benova 2014(35)

* All rates and durations are in year time units. Uniform bounds are used for parameters with greater uncertainty.

Table 6.3: Parameters that vary by GBD region*.

GBD region	Viraemic rates¥ (Sampled bounds)±	Percentage of PWID that are female (95% CI)†	HIV prevalence among PWID (95% CI)†
Central Asia	48.7% (45.2%, 52.2%)	12.6% (9.7%, 15.6%)	10.5% (8.6%, 12.5%)
Eastern Europe	69.6% (66.1%, 73.1%)	25.4% (22.0%, 28.6%)	24.7% (15.6%, 33.9%)
Australasia	74.8% (71.3%, 78.3%)	33.4% (31.0%, 35.6%)	1.1% (0.8%, 1.4%)
East and South East Asia	63.6% (60.1%, 67.1%)	20.8% (16.1%, 25.4%)	15.2% (9.9%, 20.4%)
South Asia	78.5% (75.0%, 82.0%)	3.1% (2.1%, 4.1%)	19.4% (15.0%, 23.8%)
North America	75.7% (72.2%, 79.2%)	30.0% (28.5%, 31.5%)	9.0% (7.0%, 11.1%)
Western Europe	71.0% (67.5%, 74.5%)	28.6% (12.7%, 44.4%)	4.5% (3.2%, 6.0%)
Sub-Saharan Africa	70.5% (67.0%, 74.0%)	11.6% (7.8%, 15.6%)	18.3% (11.3%, 25.4%)
Latin America	74.0% (70.5%, 77.5%)	13.0% (5.0%, 21.3%)	35.7% (15.0%, 56.6%)
Middle East and North Africa	68.8% (65.3%, 72.3%)	3.5% (2.5%, 5.2%)	3.6% (1.5%, 6.2%)

GBD: Global Burden of Disease

* Only regions from countries in the analysis are included. Parameters were sampled from triangular distributions due to the often-skewed nature of the data. The percentage of PWID that are female and the HIV prevalence among PWID are used only for estimating the rate of vertical HCV transmission.

¥ Petruzziello et al. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. 2016(285).

± Micallef et al. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. 2006(252). Note: as no bounds were available in the Petruzziello paper, bound sizes of 3.5% were taken to give the same magnitude as those from Micallef et al.

† Degenhardt et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health 2017(77).

6.4. Country inclusion criteria

Countries were considered for inclusion in the model if data were available on the population percentage of PWID, HCV prevalence for PWID, and HCV prevalence for the general population.

- For the general population, HCV prevalence estimates were taken from Blach 2017(40), and if not available for a particular country then values were taken from Gower 2014, Hope 2014, Riou 2015, and Lavanchy 2011(124, 160, 210, 309), prioritised in this order.
- For HCV prevalence among PWID, estimates were taken from Degenhardt 2017(77), and where not available were taken from Hope 2014(160) and Aceijas 2007(3), prioritising in that order.
- The estimates for the population percentage of adults that are PWID were taken from Degenhardt 2017(77), and when estimates were unavailable for a particular country were then taken from Mathers 2008, Hope 2014, Mumtaz 2014, Aceijas 2007, and Reid 2009(3, 160, 245, 258, 304), prioritised in the order given.

Subnational studies, as opposed to countries, (eg. England, rather than the UK) were omitted. The year of the estimate was recorded. Where the estimate was recorded over multiple years the model was calibrated to the middle year of the range, e.g. a serosurvey recorded from 2004-2008 would be taken as 2006.

Data were available on the population percentage of PWID, and HCV prevalence for PWID and the general population for 91 countries. Three countries were excluded. For Côte d'Ivoire and the Maldives, the HCV prevalence among PWID was unrealistically low, 1.8% and 0.7% respectively, which is lower than that of the general population. Other estimates were not available, so these two countries were omitted. For Syria, where the PWID HCV prevalence was 3.3%, the situation was similar, however, another estimate for this parameter was available (60.5%) from Nelson et al.(268), and was used instead so Syria was included in the analysis. Seychelles was also omitted from the model (in the absence of other data) as the number of infections among current PWID was higher than among the general population, due to a high estimate of the prevalence of injecting from Degenhardt et al., 2.3%(77), and a low general population HCV estimate from Lavanchy, 0.3%(210), which together are

mathematically incompatible. The prevalence data by country are shown in table 7.6. The model was calibrated to the data for these 88 countries.

6.5. Model calibration

From 1990 onwards, the model start year, a four-step calibration method using different sub-models, was used to calibrate the overall model for each country. These four sub-models were used to ease the fitting process. Table 6.4 shows the parameters that were fitted by each of the four sub-models. At each step, required model parameters were randomly sampled from their uncertainty bounds, as was data used to calibrate the sub-model, and then other unknown model parameters (see table 6.4) were estimated through fitting the sub-model to the calibration data using the Matlab function lsqnonlin. For each sampled parameter set, it was not always possible to fit the sub-models to the sampled calibration data (e.g. to the prevalence of HCV in the general population), and so these model runs were rejected. A 33% tolerance was allowed in fitting the model to a specific quantity (to match the uncertainty applied around parameters without bounds). I sampled parameter sets until 1000 full model fits were produced for each country. The step-by-step process of calibrating the model is described in detail below in sections 6.5.1-6.5.4, with model equations given in sections 6.6 and 6.7.

Table 6.4: Parameters fit by each of the four sub-models.

Sub-model	Country-specific parameters fitted
1	Population growth rates between 1990 and 2015
2	Age-specific death rates
3	The rate individuals initiate injecting
4	HCV transmission rates for the general population and PWID

6.5.1. Sub-model 1

Firstly, a simple population growth sub-model (sub-model 1) was used to calculate the average population growth rate (A) that gave the change in each countries total population size between 1990 and 2015, calibrating to population size estimates from UN datasets(380). Once the growth rate has been calibrated, if the projected population size in 2015 was not within 33% of the sampled value, then the run was rejected. After 2015, the country-specific UN predicted growth rates for 5-year intervals from 2015 up until 2040 were used.

6.5.2. Sub-model 2

Following this, the population growth sub-model was extended to incorporate three age classes (0-14, 15-34, and ≥35 years, x_1, x_2 and x_3 respectively [sub-model 2]). The model includes aging between these classes (a for aging from 0-14 to 15-34, and b for aging from 15-34 to ≥35), births and population growth (both into the 0-14 age group), and age-dependent, country-specific death rates (DR_1, DR_2, DR_3 for those aged 0-14, 15-34, and ≥35, respectively). These demographic data are taken from the UN(380) and are included so that the model could be calibrated to data on the population age distribution for each country in 2015. R(t) balances age-related mortality, while allowing for a specified rate of population growth. Sub-model 2 assumed the same level of population growth as estimated by sub-model 1, with all age-dependent deaths being balanced by additional births such that sub-model 2 has the same overall population dynamics as sub-model 1. The death rates for the youngest age group (0-14 years), DR_1, were estimated from 2015 data from the UN(380), while the death rates for the older age groups (15-34 years, DR_2, and ≥35 years, DR_3) were fitted to give the UN estimated population age distribution for each country in 2015, allowing for 33% accuracy in the proportion in each age group. For the fitting, lower bounds for the 15-34-year age-group mortality rate (DR_2) were set as 80% of the 15-34-year-old death rate taken from the UN population data, whilst the lower bound for the ≥35-year age group (DR_3) was specified as 0.0202 to equate to 49.4 years life expectancy (1/0.0202=49.4), which was deemed the upper limit for life expectancy for those aged 35 years (taken from Japan, the country with the highest life expectancy of 84.4). The upper bounds were each set very high at 0.5.

6.5.3. Sub-model 3

Sub-model 2 was then extended to include PWID, to give sub-model 3, shown in figure 6.1. As with the full model, sub-model 3 includes compartments for current injectors aged 15-34 and age ≥35, and ex-injectors aged 15-34 and ≥35. Sub-model 3 is similar to sub-model 2 in that people enter and leave the model in the same way – entering through recruitment (birth) in the 0-14 age group and leaving the model from any compartment due to age-specific death rates. However, in addition, current injectors have an additional high or low/middle-income country-specific drug-related death rate, μ, obtained from Mathers et al. WHO Bulletin 2013(246) – these were used instead of regional estimates, as not all regions had IDU death rate information available. Sub-model 3 used the parameter sets that successfully fitted the population growth and age distribution sampled data in sub-models 1 and 2. For each parameter set, the rate that individuals initiate injecting, φ, from the young adult age group (15-34 years) was calibrated to give the sampled number of PWID in each country in 2015, obtained from the distribution range from Degenhardt et al.(77) - within 33% accuracy. Each of these parameter sets also incorporated a sampled rate that PWID aged 15-34 and ≥35 cease injecting and transition into the corresponding people who used to inject drugs age class (v). This is parameterised using country-specific estimates for the duration of current injecting taken from Degenhardt et al. and presented in table 6.9(77).

6.5.4. Full model

The model parameter sets that successfully fitted sub-model 3 for each country were then used within the full model, which additionally includes HCV disease transmission and progression as described in section 6.2.2, see figure 6.2. The fourth step fitted the HCV transmission rates for the general population and PWID to give the prevalence of HCV amongst PWID and the general population (within 33% accuracy), which were both sampled from their triangular uncertainty distributions.

6.6. Model equations for sub-models used in calibration

Sub-model 1: Population growth

$$\frac{dN}{dt} = AN$$

Where A is the population growth rate, and N is the population size.

Sub-model 2: Age distributions

The model equations for the total population (x_i, for i=1, 2 and 3) in each of three age groups (0-14 for i=1, 15-34 for i=2, and ≥35 years for i=3) are given below:

$$\frac{dx_1}{dt} = R(t) - (DR_1 + a)x_1$$

$$\frac{dx_2}{dt} = ax_1 - (DR_2 + b)x_2$$

$$\frac{dx_3}{dt} = bx_2 - DR_3x_3$$

Where the recruitment rate $R(t)$ is set to balance all non-HCV and drug related deaths and also incorporates the growth rate A from sub-model 1 as follows:

$R(t) = AN + DR_1x_1 + DR_2x_2 + DR_3x_3$ where N, x_1, x_2 and x_3 all vary with time.

Sub-model 3: Prevalence of injecting drug use

Risk-group equations, for $y_1, \ldots, y_7$ – the 0-14 group, the 15-34 people who do not inject drugs group, the ≥35 people who do not inject drugs group, the 15-34 PWID group, the ≥35 PWID group, the 15-34 people who used to inject drugs group, and the ≥35 people who used to inject drugs group:

$$\frac{dy_1}{dt} = R(t) - (DR_1 + a)y_1$$

$$\frac{dy_2}{dt} = ay_1 - (DR_2 + \phi + b)y_2$$

$$\frac{dy_3}{dt} = by_2 - DR_3y_3$$

$$\frac{dy_4}{dt} = \phi y_2 - (DR_2 + \mu + v + b)y_4$$

$$\frac{dy_5}{dt} = by_4 - (DR_3 + \mu + v)y_5$$

$$\frac{dy_6}{dt} = vy_4 - (DR_2 + b)y_6$$

$$\frac{dy_7}{dt} = by_6 + vy_5 - DR_3y_7$$

where $R(t) = AN + DR_1y_1 + DR_2y_2 + DR_3y_3 + DR_2y_4 + DR_3y_5 + DR_2y_6 + DR_3y_7$

6.7. Full model equations

Subscripts 1-7 indicate the age and injecting group: 1 for aged 0-14, 2 for people who do not inject drugs (non-PWID) aged 15-34, 3 for people who do not inject drugs (non-PWID) aged ≥35, 4 for PWID aged 15-34, 5 for PWID aged ≥35, 6 for people who used to inject drugs (ex-PWID) aged 15-34, 7 for people who used to inject drugs (ex-PWID) aged ≥35.

Aged 0-14:

(1) $\frac{dS_1}{dt} = R(t) + \alpha\omega TI_1 - P(1-\delta)S_1 - (DR_1 + a)S_1$

(2) $\frac{dI_1}{dt} = V(t) + (1-\alpha)\omega TI_1 + P(1-\delta)S_1 + V(t) - (DR_1 + \lambda + \gamma + a)I_1$

(3) $\frac{dTI_1}{dt} = \lambda I_1 - (DR_1 + \omega + a)TI_1$

(4) $\frac{dCI_1}{dt} = (1-\alpha)\omega CT_1 + \gamma I_1 + P(1-\delta)CS_1 - (DR_1 + \lambda + \chi + a)CI_1$

(5) $\frac{dCT_1}{dt} = \lambda CI_1 - (DR_1 + \chi + \omega + a)CT_1$

(6) $\frac{dCS_1}{dt} = \alpha\omega CT_1 - P(1-\delta)CS_1 - (DR_1 + \varepsilon + a)CS_1$

(7) $\frac{dDI_1}{dt} = (1-\alpha)\omega DT_1 + \chi CI_1 + P(1-\delta)DS_1 - (DR_1 + \mu_4 + \lambda + a)DI_1$

(8) $\frac{dDT_1}{dt} = \lambda DI_1 + \chi CT_1 - (DR_1 + \mu_4 + \omega + a)DT_1$

(9) $\frac{dDS_1}{dt} = \alpha\omega DT_1 + \varepsilon CS_1 - P(1-\delta)DS_1 - (DR_1 + \mu_4 + a)DS_1$

Aged 15-34, non-PWID:

(10) $\frac{dS_2}{dt} = aS_1 + \alpha\omega TI_2 - P(1-\delta)S_2 - (DR_2 + \phi + b)S_2$

(11) $\frac{dI_2}{dt} = aI_1 + (1-\alpha)\omega TI_2 + P(1-\delta)S_2 - (DR_2 + \gamma + \phi + \lambda + b)I_2$

(12) $\frac{dTI_2}{dt} = aTI_1 + \lambda I_2 - (DR_2 + \phi + \omega + b)TI_2$

(13) $\frac{dCI_2}{dt} = aCI_1 + (1-\alpha)\omega CT_2 + \gamma I_2 + P(1-\delta)CS_2 - (DR_2 + \chi + \lambda + \phi + b)CI_2$

(14) $\frac{dCT_2}{dt} = aCT_1 + \lambda CI_2 - (DR_2 + \chi + \phi + \omega + b)CT_2$

(15) $\frac{dCS_2}{dt} = aCS_1 + \alpha\omega CT_2 - P(1-\delta)CS_2 - (DR_2 + \varepsilon + \phi + b)CS_2$

(16) $\frac{dDI_2}{dt} = aDI_1 + (1-\alpha)\omega DT_2 + \chi CI_2 + P(1-\delta)DS_2 - (DR_2 + \mu_4 + \phi + \lambda + b)DI_2$

(17) $\frac{dDT_2}{dt} = aDT_1 + \chi CT_2 + \lambda DI_2 - (DR_2 + \mu_4 + \phi + \omega + b)DT_2$

(18) $\frac{dDS_2}{dt} = aDS_1 + \alpha\omega DT_2 + \varepsilon CS_2 - P(1-\delta)DS_2 - (DR_2 + \mu_4 + \phi + b)DS_2$

Aged 35+, non-PWID:

(19) $\frac{dS_3}{dt} = bS_2 + \alpha\omega TI_3 - P(1-\delta)S_3 - DR_3 S_3$

(20) $\frac{dI_3}{dt} = bI_2 + (1-\alpha)\omega TI_3 + P(1-\delta)S_3 - (DR_3 + \gamma + \lambda)I_3$

(21) $\frac{dTI_3}{dt} = bTI_2 + \lambda I_3 - (DR_3 + \omega)TI_3$

(22) $\frac{dCI_3}{dt} = bCI_2 + (1-\alpha)\omega CT_3 + \gamma I_3 + P(1-\delta)CS_3 - (DR_3 + \chi + \lambda)CI_3$

(23) $\frac{dCT_3}{dt} = bCT_2 + \lambda CI_3 - (DR_3 + \omega + \chi)CT_3$

(24) $\frac{dCS_3}{dt} = bCS_2 + \alpha\omega CT_3 - P(1-\delta)CS_3 - (DR_3 + \varepsilon)CS_3$

(25) $\frac{dDI_3}{dt} = bDI_2 + (1-\alpha)\omega DT_3 + \chi CI_3 + P(1-\delta)DS_3 - (DR_3 + \mu_4 + \lambda)DI_3$

(26) $\frac{dDT_3}{dt} = bDT_2 + \lambda DI_3 + \chi CT_3 - (DR_3 + \mu_4 + \omega)DT_3$

(27) $\frac{dDS_3}{dt} = bDS_2 + \alpha\omega DT_3 + \varepsilon CS_3 - P(1-\delta)DS_3 - (DR_3 + \mu_4)DS_3$

Aged 15-34, PWID:

(28) $\frac{dS_4}{dt} = \phi S_2 + \alpha\omega TI_4 - (P + \pi)(1-\delta)S_4 - (DR_2 + \mu + v + b)S_4$

(29) $\frac{dI_4}{dt} = \phi I_2 + (1-\alpha)\omega TI_4 + (P+\ \pi)(1-\delta)S_4 - (DR_2 + \mu + \gamma + \lambda + v + b)I_4$

(30) $\frac{dTI_4}{dt} = \phi TI_2 + \lambda I_4 - (DR_2 + \mu + \omega + v + b)TI_4$

(31) $\frac{dCI_4}{dt} = \phi CI_2 + (1-\alpha)\omega CT_4 + \gamma I_4 + (P+\ \pi)(1-\delta)CS_4 - (DR_2 + \mu + \chi + \lambda + v + .b)CI_4$

(32) $\frac{dCT_4}{dt} = \phi CT_2 + \lambda CI_4 - (DR_2 + \mu + \omega + \chi + v + b)CT_4$

(33) $\frac{dCS_4}{dt} = \phi CS_2 + \alpha\omega CT_4 - (P+\ \pi)(1-\delta)CS_4 - (DR_2 + \mu + \varepsilon + v + b)CS_4$

(34) $\frac{dDI_4}{dt} = \phi DI_2 + (1-\alpha)\omega DT_4 + \chi CI_4 + (P+\ \pi)(1-\delta)DS_4 - (DR_2 + \mu + \mu_4 + \lambda + v + b)DI_4$

(35) $\frac{dDT_4}{dt} = \phi DT_2 + \chi CT_4 + \lambda DI_4 - (DR_2 + \mu + \mu_4 + \omega + v + b)DT_4$

(36) $\frac{dDS_4}{dt} = \phi DS_2 + \alpha\omega DT_4 + \varepsilon CS_4 - (P+\ \pi)(1-\delta)DS_4 - (DR_2 + \mu + \mu_4 + v + b)DS_4$

Aged 35+, PWID:

(37) $\frac{dS_5}{dt} = bS_4 + \alpha\omega TI_5 - (P+\ \pi)(1-\delta)S_5 - (DR_3 + \mu + v)S_5$

(38) $\frac{dI_5}{dt} = bI_4 + (1-\alpha)\omega TI_5 + (P+\ \pi)(1-\delta)S_5 - (DR_3 + \mu + \gamma + \lambda + v)I_5$

(39) $\frac{dTI_5}{dt} = bTI_4 + \lambda I_5 - (DR_3 + \mu + \omega + v)TI_5$

(40) $\frac{dCI_5}{dt} = bCI_4 + (1-\alpha)\omega CT_5 + \gamma I_5 + (P+\ \pi)(1-\delta)CS_5 - (DR_3 + \mu + \chi + \lambda + v)CI_5$

(41) $\frac{dCT_5}{dt} = bCT_4 + \lambda CI_5 - (DR_3 + \mu + \omega + \chi + v)CT_5$

(42) $\frac{dCS_5}{dt} = bCS_4 + \alpha\omega CT_5 - (P+\ \pi)(1-\delta)CS_5 - (DR_3 + \mu + \varepsilon + v)CS_5$

(43) $\frac{dDI_5}{dt} = bDI_4 + (1-\alpha)\omega DT_5 + \chi CI_5 + (P+\ \pi)(1-\delta)DS_5 - (DR_3 + \mu + \mu_4 + \lambda + v)DI_5$

(44) $\frac{dDT_5}{dt} = bDT_4 + \chi CT_5 + \lambda DI_5 - (DR_3 + \mu + \mu_4 + \omega + v)DT_5$

(45) $\frac{dDS_5}{dt} = bDS_4 + \alpha\omega DT_5 + \varepsilon CS_5 - (P+\ \pi)(1-\delta)DS_5 - (DR_3 + \mu + \mu_4 + v)DS_5$

Aged 15-34, ex-PWID:

(46) $\frac{dS_6}{dt} = vS_4 + \alpha\omega TI_6 - P(1-\delta)S_6 - (DR_2 + b)S_6$

(47) $\frac{dI_6}{dt} = vI_4 + (1-\alpha)\omega TI_6 + P(1-\delta)S_6 - (DR_2 + \gamma + \lambda + b)I_6$

(48) $\frac{dTI_6}{dt} = vTI_4 + \lambda I_6 - (DR_2 + \omega + b)TI_6$

(49) $\frac{dCI_6}{dt} = vCI_4 + (1-\alpha)\omega CT_6 + \gamma I_6 + P(1-\delta)CS_6 - (DR_2 + \chi + \lambda + b)CI_6$

(50) $\frac{dCT_6}{dt} = vCT_4 + \lambda CI_6 - (DR_2 + \chi + \omega + b)CT_6$

(51) $\frac{dCS_6}{dt} = vCS_4 + \alpha\omega CT_6 - P(1-\delta)CS_6 - (DR_2 + \varepsilon + b)CS_6$

(52) $\frac{dDI_6}{dt} = vDI_4 + (1-\alpha)\omega DT_6 + \chi CI_6 + P(1-\delta)DS_6 - (DR_2 + \mu_4 + \lambda + b)DI_6$

(53) $\frac{dDT_6}{dt} = vDT_4 + \lambda DI_6 + \chi CT_6 - (DR_2 + \mu_4 + \omega + b)DT_6$

(54) $\frac{dDS_6}{dt} = vDS_4 + \alpha\omega DT_6 + \varepsilon CS_6 - P(1-\delta)DS_6 - (DR_2 + \mu_4 + b)DS_6$

Aged 35+, ex-PWID:

(55) $\frac{dS_7}{dt} = bS_6 + \alpha\omega TI_7 + vS_5 - P(1-\delta)S_7 - DR_3S_7$

(56) $\frac{dI_7}{dt} = bI_6 + (1-\alpha)\omega TI_7 + vI_5 + P(1-\delta)S_7 - (DR_3 + \gamma + \lambda)I_7$

(57) $\frac{dTI_7}{dt} = bTI_6 + vTI_5 + \lambda I_7 - (DR_3 + \omega)TI_7$

(58) $\frac{dCI_7}{dt} = bCI_6 + (1-\alpha)\omega CT_7 + \gamma I_7 + vCI_5 + P(1-\delta)CS_7 - (DR_3 + \chi + \lambda)CI_7$

(59) $\frac{dCT_7}{dt} = bCT_6 + vCT_5 + \lambda CI_7 - (DR_3 + \chi + \omega)CT_7$

(60) $\frac{dCS_7}{dt} = bCS_6 + \alpha\omega CT_7 + vCS_5 - P(1-\delta)CS_7 - (DR_3 + \varepsilon)CS_7$

(61) $\frac{dDI_7}{dt} = bDI_6 + (1-\alpha)\omega DT_7 + \chi CI_7 + vDI_5 + P(1-\delta)DS_7 - (DR_3 + \mu_4 + \lambda)DI_7$

(62) $\frac{dDT_7}{dt} = bDT_6 + vDT_5 + \lambda DI_7 + \chi CT_7 - (DR_3 + \mu_4 + \omega)DT_7$

(63) $\frac{dDS_7}{dt} = bDS_6 + \alpha\omega DT_7 + vDS_5 + \varepsilon CS_7 - P(1-\delta)DS_7 - (DR_3 + \mu_4)DS_7$

The birth rate R(t) is set to balance all non-HCV related and non-drug related deaths while also incorporating the time-varying population growth rate A, and time-varying population size N, as follows:

$$R(t) = AN + DR_1Y_1 + DR_2(Y_2 + Y_4 + Y_6) + DR_3(Y_3 + Y_5 + Y_7) - V(t)$$

where for each age group i defined by sub-model 3 I define

$$Y_i = S_i + I_i + TI_i + CI_i + CT_i + CS_i + DI_i + DT_i + DS_i$$

and V(t) is the number of chronically infected births due to vertical transmission, described in section 6.8.

6.8. Vertical transmission of HCV calculations

To calculate the number of chronically infected births due to vertical transmission, vertical transmission rates for HCV, varying by whether a woman is HIV-coinfected or not (HIV prevalences for women aged 15-24 taken from the World Bank(365)), are multiplied by the estimated number of HCV-infected women aged 15-34 years in each of the four possible combinations of ever/never being PWID, and being HIV-coinfected or not, see the table below. These are then summed and multiplied by the region-specific fertility rate (F: the average number of childbirths a woman of childbearing age will have) divided by 20 (giving the births per year in the 15-34 age category) to produce the estimated number of HCV infected births each year. Although some births will occur among women of other ages, most will occur in this age group and so we associate all the births to this group. Fertility was assumed to be the same between female PWID and non-injectors.

V(t) is defined: $V(t) = (e_3 q_2 + e_4 q_1 + e_5 q_2 + e_6 q_1)\frac{F}{20}$

where parameter definitions are given in table 6.5.

Table 6.5: Calculations for the vertical transmission rate.

Term	Description
$e_1 = (I_2 + CI_2 + DI_2)/2$	The number of HCV infected women aged 15-34 years old that have never been PWID*
$e_2 = (I_4 + CI_4 + DI_4 + I_6 + CI_6 + DI_6)R_F$ where R_F is the region-specific percentage of PWID that are female	The number of HCV infected women aged 15-34 years old that have ever been PWID
$e_3 = e_1 C_H$ where C_H is the country-specific HIV prevalence for young women (aged 15-24)	The number of HCV infected women aged 15-34 years old that have never been PWID that are coinfected with HIV
$e_4 = e_2 R_H$ where R_H is the region-specific HIV prevalence among PWID	The number of HCV infected women aged 15-34 years old that have ever been PWID that are coinfected with HIV
$e_5 = e_1 - e_3$	The number of HCV infected women aged 15-34 years old that have never been PWID that are not coinfected with HIV
$e_6 = e_2 - e_4$	The number of HCV infected women aged 15-34 years old that have ever been PWID that are not coinfected with HIV
q_1	Probability of vertical transmission of HCV RNA confirmed infection per birth among women with HCV RNA that are HIV negative.
q_2	Probability of vertical transmission of HCV RNA confirmed infection per birth among women with HCV RNA that are HIV negative.

*The distribution of HCV among people that have never injected drugs is assumed to be even between men and women.

6.9. Forces of infection

For the different forces of infection, I have:

Size of total population:

$$N = \sum_{i=1}^{7} S_i + I_i + TI_i + CI_i + CT_i + CS_i + DI_i + DT_i + DS_i$$

Size of the PWID population:

$$N_I = \sum_{i=4}^{5} S_i + I_i + TI_i + CI_i + CT_i + CS_i + DI_i + DT_i + DS_i$$

The proportion of the population that are infected:

$$\xi = (I_1 + CI_1 + DI_1 + I_2 + CI_2 + DI_2 + I_3 + CI_3 + DI_3 + I_4 + CI_4 + DI_4 + I_5 + CI_5 + DI_5 + I_6 + CI_6 + DI_6 + I_7 + CI_7 + DI_7)/N$$

The force of infection for the whole population:

$$P = \beta\xi$$

where β is the transmission rate in the general population. The additional force of infection which acts on PWID is given by:

$$\pi = \theta(I_4 + I_5 + CI_4 + CI_5 + DI_4 + DI_5)/N_I$$

where θ is the additional transmission rate due to injecting. The transmission rate in the general population (β) and PWID population (θ), are found by solving the model equations (1-63) and calibrating the prevalence of chronic HCV amongst PWID and the general population in the model to the PWID and general population chronic HCV prevalence from the data, respectively.

6.10. HCV epidemic trajectory assumptions

To determine the trajectory of country-level epidemics, it is important to assess both whether there is evidence for changes in HCV prevalence or incidence over time, but also whether there have been any major changes in the prevalence or frequency of important risk behaviours or interventions. Section 2.3 discussed HCV transmission in detail.

6.10.1. Changes in HCV risk behaviours

HCV is transmitted through several known risk behaviours, principally unscreened blood donations, unsafe medical injections, and IDU. Evidence suggests the risk of receiving an HCV-infected blood transfusion has decreased over time following the introduction of blood donation safety guidelines and improved screening practices, with some estimates for developing countries suggesting a decline from 1/50 transfusions in the late 1980s to 1/200,000 transfusions in 2000(291). However, this same review from 2006 states that such a decline had not occurred in many low and middle income countries by the early 2000s(291). Since then, a 2016 WHO report stated that 174 of 180 countries report a policy of testing all blood for HCV(399), an improvement from 107 out of 148 in 2006(362). The UK introduced screening guidelines for HCV in 1991(363), whereas many countries in the South Asia region (which has the highest number of infections) introduced such guidelines in the early 2000s(64), whilst guideline introductions tended to be later in Africa, for example 2005 in Ethiopia(329), and 2006 in Nigeria(18). The introduction of these guidelines has brought progress, although in many countries blood donation safety could still be improved(178).

Similarly to the reduction seen in the transmission risk for blood transfusions, the HCV transmission risk due to unsafe medical injections has also decreased since 2000(283), which followed an emphasis on preventing re-use of syringes led by the Safe Injection Global Network (SIGN)(394). Using population surveys, injection safety assessments and published studies, Pepin et al. found that the re-use of injection devices fell from 39.8% of all syringes in 2000, to 5.5% in 2010(282). Subsequently, using a mass action model and these estimates, Pepin et al. estimated that between these years there was an 83% reduction in new HCV infections transmitted through medical injections, although there was heterogeneity in the sources of data used for the two time points(283). To calculate this, Pepin et al used HCV prevalence data from a study by Hanafiah et al.(142), which was perhaps the first study to

estimate the trajectory of the HCV epidemic at the regional and global level, and is discussed in section 6.10.2(142).

The main interventions for reducing HCV transmission among PWID, a group with particularly high prevalence and incidence of HCV(77), are needle and syringe programmes and opioid substitution therapy(287). Larney et al. performed a systematic review of the number of countries implementing these interventions and found an increase from 2010 to 2017 for both; from 81 to 93 countries for needle and syringe programmes, and from 70 to 86 countries for opioid substitution therapy(209). Theoretically this would indicate a reduction in HCV transmission risk for PWID, however, the review notes that the coverage of these interventions is generally too poor to prevent HCV epidemics among PWID.

Aside from the already discussed interventions, there is not enough evidence for the effectiveness of other interventions to reduce HCV transmission risk, especially community-based risks, which are wide ranging and uncertain(13, 219, 321).

6.10.2. Changes in HCV epidemic data

The gold standard measure for assessing changes in an epidemic trajectory is observing changes in the incidence of infection over time. However, incidence estimates are rare even amongst PWID, for whom infections are more common, and so we generally must rely on changes in HCV prevalence over time for determining whether HCV epidemics are expanding or in decline. Several studies have done this for HCV, which are described below.

As mentioned in section 6.10.1, Hanafiah et al. undertook a systematic review and meta-analysis of general population HCV prevalence estimates (excluding grey literature and non-English language studies), splitting studies performed before and after 1997 as early (ascribed to 1990) and late (ascribed to 2005), and estimated the HCV epidemic trajectories by comparing these pooled prevalence estimates(142). In this study, global anti-HCV prevalence increased from 2.3% to 2.8% between 1990 and 2005. These trajectories varied by region, but for most there was no statistical change in HCV prevalence between the time points. Such a method for determining a change in prevalence is limited by heterogeneity between the studies included in each time point (1990 and 2005) and is particularly sensitive to these differences at regional levels where the same countries may not contribute data for

both time points. Notably a study could be included in the estimate for 2005 if it occurred in 1998, which was before blood donation safety guidelines were introduced in many countries, and before the reduction in the re-use of medical injections(282, 291).

The Global Burden of Disease study modelled changes in the burden of disease due to HCV between 1990 and 2013 and found an increase in deaths and life years lost. However, they did not present how HCV prevalence had changed between these time points(347). Importantly, mortality can still increase with a stable or decreasing epidemic and so these projections are not useful for understanding the overall epidemic dynamics.

Recently, Blach et al. modelled and presented the change in viremic HCV prevalence globally and by region between 1980 to 2015, based on changes in age-specific HCV prevalence over time(40). Globally, they estimated the total number of viremic infections to be around 36 million in 1980, which increased to around 71 million by 2000 and then remained steady until 2015. When accounting for the increasing global population this means an increase from around 0.8% viremic HCV prevalence in 1980, to around 1.2% in 2000, decreasing to around 1.0% by 2015. These numbers were estimated approximately off published graphs as the exact numbers were not made available (UN global population numbers were used as the denominator). These HCV epidemic trajectories vary by region (after accounting for population changes), with decreases in most regions from 1990 onwards, but with increases estimated in Eastern Europe, Australasia, and South and Central Asia. Estimations of the prevalence changes by region from the paper by Blach et al. are shown in table 6.5 (regional populations were taken from the Global Burden of Disease study). The regional numbers were not made explicitly available in their paper and the estimates could not be accurately obtained from the regional graphs. Additionally, the uncertainty around these estimates was not given. The analysis by Blach et al. used a Markov model starting from 1950 when there is assumed to be negligible HCV infections, with the epidemic increasing from then. However, there is uncertainty in these modelled HCV prevalence trends. Many countries in the analysis only have one data point on HCV prevalence, making it hard to determine trajectory. Additionally, for some countries, expert opinion, which is generally considered the lowest grade of evidence(416), is relied on for determining how the epidemics may be evolving rather than data. More generally, there is a lack of data feeding into the Blach model for less recent time-points, with less robust data available in more recent years, meaning there is uncertainty regarding the trajectory of the

epidemic used in that model, which is not discussed. Only Egypt(93, 181), France(85, 249), and the USA(15, 78) have two HCV prevalence surveys for the general population that were described as robust by Blach et al.(40) – all of which suggested a decreasing trend. Only two other countries (China and Thailand) had multiple surveys, but they were not considered robust enough (possibly regarding comparability between survey methods) by Blach et al., although they also suggested a decreasing trend of prevalence.

6.10.3. HCV epidemic trajectories among PWID

Regarding the trajectory of the HCV epidemics among PWID, data were available from the latest review by Degenhardt et al(77). Prevalence estimates from surveys among PWID were compared across time for each region, and overall. For most regions there was insufficient power to look at trends over time, and for others no change over time was detected. For East and South East Asia and North America, a decreasing trend was detected. For East and South East Asia, the change in prevalence was driven by studies in China, when China was omitted there was no reduction in prevalence in East and South East Asia. However, China itself is vast and heterogeneous, and the studies were across various regions of China – only one was national, so the decrease seen is not necessarily a robust assumption. Data from the Degenhardt review suggests there is evidence for a decrease in HCV prevalence among PWID in North America. However, conflicting evidence from the US (which makes up 90% of the population of North America) show acute incident cases are increasing, as reviewed by Shiffman(57, 330), suggesting a recent increasing epidemic in this setting. The data in the Degenhardt review are mostly from studies before this recent upturn in infections in the US, so this is investigated in sensitivity analyses. All sensitivity analyses are listed in sections 7.2.2 and 8.2.3.

Table 6.6: Regional changes in viraemic prevalence from 1990 to 2015, estimated from Blach et al.(40) using GBD regional categories and population sizes.

	Viraemic population (millions)		Total population (millions)		Viraemic prevalence		
Region	1990	2015	1990	2015	1990	2015	Annual Change
Asia, Central	1.1	3.3	68.8	87.0	1.6%	3.8%	5.49%
Asia, East	10.8	10.5	1194.9	1432.9	0.9%	0.7%	-0.76%
Asia Pacific, High Income	3.1	1.2	168.9	182.9	1.8%	0.7%	-2.57%
Asia, South	9	15.3	1103.9	1691.0	0.8%	0.9%	0.44%
Asia, Southeast	3.1	4.7	461.5	651.0	0.7%	0.7%	0.30%
Australasia	0.1	0.2	20.4	28.9	0.5%	0.7%	1.65%
Caribbean	0.2	0.3	35.8	45.3	0.6%	0.7%	0.74%
Europe, Central	0.7	1.2	123.1	116.7	0.6%	1.0%	3.24%
Europe, Eastern	3.5	6.7	221.2	215.0	1.6%	3.1%	3.88%
Europe, Western	2.1	2.3	381.3	433.6	0.6%	0.5%	-0.15%
Latin America, Andean	0.3	0.4	39.0	58.3	0.8%	0.7%	-0.44%
Latin America, Central	1.1	1.3	169.0	251.8	0.7%	0.5%	-0.83%
Latin America, Southern	0.4	0.4	49.0	64.8	0.8%	0.6%	-0.98%
Latin America, Tropical	1.9	1.9	154.8	214.5	1.2%	0.9%	-1.11%
North America, High Income	3.5	3.1	277.7	359.9	1.3%	0.9%	-1.27%
North Africa/Middle East	8	8.5	336.1	566.2	2.4%	1.5%	-1.48%
Oceania	0.1	0.1	6.6	11.0	1.5%	0.9%	-1.59%
Sub-Saharan Africa, Central	2.4	2.3	53.1	114.8	4.5%	2.0%	-2.23%
Sub-Saharan Africa, East	1.3	2.1	186.1	377.0	0.7%	0.6%	-0.81%
Sub-Saharan Africa, Southern	0.6	0.6	53.4	77.4	1.1%	0.8%	-1.24%
Sub-Saharan Africa, West	3	5.1	198.7	391.1	1.5%	1.3%	-0.55%

GBD: Global Burden of Disease

6.10.4. Conclusions for the HCV epidemic assumptions

In summary, evidence suggests levels of transmission risk due to blood transfusions(291) and re-use of medical injections(283) have decreased since 2000, with Blach et al.'s review(40) and modelling also suggesting that the global prevalence of infection has decreased by around 17% from 2000 to 2015. Conversely, HCV prevalence was stable or may have increased slightly up to the early 2000s (based on Blach(40) and Hanafiah(142)),

although there is greater uncertainty around the trajectory of the epidemic at this time. Accounting for this evidence on decreases in risk behaviours and HCV prevalence, the most likely scenario is that the global HCV epidemic is decreasing slowly, with possible variations by region, although there is not robust evidence to calculate these regional changes.

For my model, I assume a slow decrease in the general population HCV epidemic over time. This was accounted for by seeding the initial modelled HCV prevalence (1990) in the setting as higher than the prevalence estimate we are fitting to, with the model then calibrating a force of infection to result in a decreasing HCV epidemic to fit the estimate for the general population HCV prevalence. Specifically, the HCV prevalence in the general population in 1990 was seeded as 1.13% (17% decline over 15 years) higher for each year between 1990 and when the general population HCV prevalence estimate was available for each country. For example, if the estimate was taken from 2005, 15 years after 1990, then the seeded HCV prevalence was set to be (100+(1.13*15)) = 116.95% of the 2005 value. However, due to the poor data used in making this assumption I assumed large uncertainty bounds around this estimate of decrease between 0% and 1.5% per year. I also examine in sensitivity analyses how my results would vary if I assumed a stable HCV epidemic or regional variations in annual change in HCV prevalence as given in table 6.5 using the same method as described above.

For, Egypt(93, 181), France(85, 249) and USA(15, 78), where multiple robust and comparable surveys exist, a separate method was used, section 6.2.6. The available information about the trajectory of the HCV epidemics among PWID shows great uncertainty, due to this I assumed the epidemic among PWID to be stable, but this assumption is also tested in my model using sensitivity analyses that assume a decrease in HCV prevalence among PWID at the same rate as in the general population.

6.10.5. Assumptions around the population percentage of PWID among adults

The population percentage of PWID among adults was assumed to be stable between 1990 and the year of the estimate due to a lack of robust information about these trends in most countries. For Sub-Saharan African and Eastern European countries evidence suggests IDU in these regions expanded later than in other settings(96, 119), so in 1990 I assumed this proportion to be 25% of the value in the study year. A sensitivity analysis was performed to

test the effect of removing the assumption of later IDU epidemics in Sub-Saharan Africa and Eastern Europe. A sensitivity analysis also investigated the effect of an increasing proportion of adults that are PWID in the US. See sections 7.2.2 and 8.2.3 for information about sensitivity analyses performed.

6.11. Alternative model structure for Egypt, France, and USA

The extra information from the multiple surveys on the direction of the general population HCV epidemic for Egypt(93, 181), France(85, 249), and USA(15, 78) was incorporated into the modelling for these countries by using a slightly different calibration technique to other countries.

For Egypt, the two anti-HCV survey values used were 14.7% (95% confidence interval: 14.1%, 15.4%) in 2008 and 10.0% (95% confidence interval: 9.5%, 10.5%) in 2015, whilst for France the values were 1.05% (95% confidence interval: 0.75%, 1.34%) in 1994 and 0.84% (95% confidence interval: 0.65, 1.10%) in 2004, and 1.8% (95% confidence interval: 1.5%, 2.3%) for 1994 and 1.3% (1.2%, 1.5%) in 2010 for the USA. For each of these three countries the model was calibrated to the first survey value (in the year of the general population survey) to produce a general population transmission rate. The general population transmission rate was then adjusted by multiplying it by a random number between 0 and 1 from the year of the first survey onwards. Runs were accepted if the general population chronic HCV prevalence was ±33% of the 2nd survey sampled HCV prevalence estimate, as well as ±33% relative to the PWID HCV prevalence estimate.

6.12. Detailed data issues

A revised, lower estimate for the population percentage of PWID in Canada from Grebely 2018(127) was used instead of Degenhardt 2017(77) – 0.39% (Uncertainty interval: 0.31%, 0.47%) instead of 1.22% (Uncertainty interval: 1.04%, 1.40%). Both papers utilise data from the same systematic review but the data point in Grebely is updated. For Spain and Netherlands, the population percentage of PWID, 0.03%, appeared low for Western European countries. For these countries, the PWID prevalence estimates were investigated further using information on the number of PWID on OST. For Netherlands, the total

number of people on OST was very low(98) so the estimate of 0.03% was accepted. For Spain, a 2011 estimate suggested 15,000 OST admissions for people with heroin dependence, which was combined with a back-calculation based on 60% of PWID reporting being on OST(97). This method gave an updated estimate of 25,000 PWID, and an updated population percentage of PWID of 0.075% for Spain. Bounds of ±33% were added to this point estimate.

For Cyprus, Estonia, FYR Macedonia, Iceland, Luxembourg, Malta, Montenegro, and Slovenia, the UN does not have detailed enough information about age-specific general population death rates for 2010-15. This is because numbers of deaths are rounded to the nearest 1,000, meaning for some countries with a low number of deaths the mortality rate appears to be 0 for some age categories in this period, or more recent time periods in general. For these countries, estimates for death rates were taken from other nearby countries that appear to have similar death rates for previous time periods and age categories – Greece, Latvia, Greece, Sweden, France, Italy, Serbia, and Austria were used, respectively.

For Turkmenistan's estimate of HCV prevalence among PWID from Aceijas 2007(3), only the bounds (46.2%, 75.0%) were available so the mid-point was taken (60.6%). For Finland's estimate of HCV prevalence among the general population from Blach 2017(40), the mid-point given (0.5%) does not fit within the given bounds (0.6%, 0.9%). Therefore, I took the midpoint (0.7%) to which the bounds applied - from Gower 2014. For several general population HCV estimates from Blach 2017(40), one or both of the lower or upper bounds given do not fit around the point estimate given, so I replaced these bounds by ±33% of the point estimate. This was for Colombia and Luxembourg (both upper), Thailand (lower), and Saudi Arabia (both). For Pakistan's general population HCV prevalence estimate from Blach 2017(40), the bounds did not fit around the estimate so were instead taken from the national survey(295). National survey data were also used for Georgia's general population HCV prevalence estimate (the same source used in Blach 2017)(132).

The injecting duration estimates for Afghanistan (2.8 years), and Turkey (3 years), appeared low so these were adjusted to their respective regional estimates, 6.4 years and 7.8 years, respectively, with the lower estimates being used as the lower bound to the sampling interval, while the upper bound of the sampling interval was estimated by multiplying the higher estimates by 2, as was the procedure for other countries.

6.13. Country-level data

Table 6.7 gives the country-level data on population sizes, age distributions, mortality rates, fertility rates, and prevalences of HIV among females aged 15-24, that were used to parameterise the model.

Country-level sampled ranges for antibody prevalence of HCV among the general population and PWID, as well as the population percentage of PWID among adults are given in table 6.8. Table 6.8 also includes the estimate source, year, and grade (discussed further in section 6.14), where available.

Country-level injecting durations are given in table 6.9, whilst table 6.10 gives country-level historical treatment numbers.

Table 6.7: Sampled population sizes, age distributions, mortality rates by age-group, fertility rates, and HIV prevalences for women aged 15-24 by country*.

Country	Population (1000s)		1990 age distributions (proportions)			2015 age distributions (proportions)			Mortality rates per 100 person years, 2015, age:		Fertility rates 2015 (lifetime births per woman)	Female (15-24) HIV % 2016
	1990	2015	0-14	15-34	≥35	0-14	15-34	≥35	0-14	15-34		
Afghanistan	12249	32526	0.48	0.32	0.20	0.44	0.35	0.21	0.857	0.288	5.26	0.10
Albania	3281	2925	0.33	0.36	0.31	0.18	0.30	0.52	0.114	0.068	1.71	0.10
Argentina	32729	43416	0.31	0.30	0.39	0.25	0.31	0.44	0.128	0.089	2.34	0.10
Armenia	3538	3018	0.30	0.35	0.35	0.18	0.32	0.49	0.108	0.062	1.65	0.10
Australia	17041	23970	0.22	0.33	0.45	0.19	0.28	0.53	0.040	0.045	1.88	0.10
Austria	7724	8542	0.17	0.31	0.52	0.14	0.25	0.61	0.033	0.038	1.45	0.00
Azerbaijan	7243	9753	0.33	0.37	0.30	0.22	0.35	0.43	0.430	0.081	2.10	0.10
Bangladesh	106189	160995	0.42	0.35	0.23	0.29	0.37	0.34	0.327	0.097	2.22	0.10
Belarus	10216	9496	0.23	0.30	0.47	0.16	0.27	0.56	0.052	0.161	1.64	0.20
Belgium	10006	11301	0.18	0.30	0.52	0.17	0.24	0.59	0.031	0.051	1.78	0.00
Bosnia	4463	3810	0.24	0.35	0.41	0.13	0.27	0.59	0.078	0.058	1.31	0.00
Brazil	149352	207846	0.35	0.36	0.29	0.23	0.33	0.44	0.179	0.141	1.78	0.20
Bulgaria	8841	7149	0.20	0.27	0.52	0.14	0.23	0.63	0.079	0.084	1.51	0.10
Canada	27690	35942	0.21	0.33	0.46	0.16	0.27	0.57	0.045	0.048	1.61	0.00
China	1172442	1376048	0.29	0.38	0.33	0.17	0.30	0.53	0.116	0.065	1.60	0.00
Croatia	4776	4242	0.20	0.29	0.51	0.15	0.24	0.61	0.032	0.058	1.49	0.10
Cyprus	767	1165	0.25	0.33	0.42	0.17	0.32	0.51	0.025	0.056	1.38	0.00
Czech Republic	10341	10544	0.22	0.28	0.50	0.15	0.24	0.61	0.025	0.064	1.48	0.10
Denmark	5141	5668	0.17	0.30	0.53	0.17	0.25	0.58	0.021	0.043	1.73	0.00
Egypt	57412	91507	0.41	0.32	0.27	0.33	0.34	0.32	0.218	0.091	3.38	0.10
Estonia	1565	1311	0.22	0.29	0.49	0.16	0.25	0.59	0.068	0.123	1.59	0.00
Finland	4996	5504	0.19	0.28	0.52	0.16	0.24	0.59	0.022	0.059	1.77	0.00
France	56957	64395	0.20	0.30	0.50	0.18	0.24	0.58	0.032	0.046	1.98	0.10
FYROM	1996	2079	0.26	0.33	0.41	0.17	0.30	0.54	0.057	0.056	1.50	0.10
Georgia	5410	3998	0.25	0.31	0.44	0.17	0.29	0.53	0.144	0.086	2.00	0.10
Germany	79116	80687	0.16	0.30	0.54	0.13	0.23	0.64	0.031	0.037	1.43	0.00

Country	Population (1000s)		1990 age distributions (proportions)			2015 age distributions (proportions)			Mortality rates per 100 person years, 2015, age:		Fertility rates 2015 (lifetime births per woman)	Female (15-24) HIV % 2016
	1990	2015	0-14	15-34	≥35	0-14	15-34	≥35	0-14	15-34		
Ghana	14628	27411	0.44	0.34	0.22	0.39	0.35	0.26	0.754	0.331	4.18	1.00
Greece	10248	10955	0.20	0.30	0.50	0.15	0.23	0.63	0.025	0.056	1.34	0.00
Hungary	10377	9856	0.20	0.27	0.52	0.15	0.25	0.61	0.042	0.057	1.33	0.00
Iceland	255	331	0.25	0.33	0.42	0.20	0.28	0.52	0.024	0.049	1.98	0.00
India	870129	1311049	0.38	0.34	0.28	0.29	0.35	0.36	0.423	0.176	2.44	0.10
Indonesia	181437	257563	0.36	0.37	0.27	0.28	0.33	0.39	0.258	0.159	2.45	0.20
Iran	56226	79108	0.45	0.32	0.23	0.24	0.39	0.37	0.145	0.086	1.75	0.10
Ireland	3569	4688	0.28	0.31	0.41	0.22	0.25	0.53	0.020	0.068	2.00	0.10
Israel	4500	8066	0.31	0.32	0.37	0.28	0.29	0.43	0.036	0.035	3.04	0.00
Italy	57125	59796	0.16	0.31	0.53	0.14	0.20	0.66	0.022	0.036	1.43	0.10
Japan	124513	126575	0.18	0.28	0.53	0.13	0.21	0.66	0.026	0.044	1.41	0.00
Kazakhstan	16539	17624	0.31	0.34	0.34	0.27	0.32	0.41	0.157	0.172	2.70	0.10
Kenya	23402	46052	0.49	0.33	0.18	0.42	0.36	0.22	0.774	0.418	4.10	3.50
Kyrgyzstan	4373	5941	0.37	0.34	0.28	0.31	0.36	0.33	0.214	0.113	3.12	0.10
Latvia	2664	1971	0.21	0.29	0.49	0.15	0.25	0.60	0.068	0.124	1.50	0.30
Lebanon	2703	5851	0.34	0.34	0.31	0.24	0.37	0.39	0.071	0.037	1.72	0.10
Libya	4437	6279	0.42	0.35	0.23	0.30	0.33	0.37	0.235	0.135	2.40	0.00
Lithuania	3696	2880	0.23	0.31	0.46	0.15	0.25	0.60	0.048	0.138	1.59	0.10
Luxembourg	382	568	0.17	0.30	0.52	0.16	0.27	0.56	0.032	0.046	1.55	0.00
Madagascar	11599	24234	0.46	0.33	0.21	0.42	0.35	0.24	0.531	0.251	4.40	0.10
Malaysia	18038	30331	0.37	0.36	0.27	0.25	0.37	0.38	0.073	0.083	2.11	0.10
Malta	364	429	0.23	0.30	0.47	0.14	0.27	0.59	0.022	0.036	1.41	0.10
Mauritius	1056	1276	0.29	0.39	0.32	0.19	0.30	0.50	0.081	0.103	1.49	0.00
Mexico	85355	127016	0.39	0.36	0.25	0.28	0.34	0.38	0.181	0.100	2.29	0.10
Moldova	4364	4070	0.28	0.31	0.41	0.16	0.33	0.51	0.094	0.088	1.27	0.20
Montenegro	615	627	0.25	0.33	0.42	0.18	0.28	0.54	0.069	0.061	1.71	0.20
Morocco	24879	34377	0.40	0.36	0.24	0.27	0.34	0.38	0.250	0.056	2.60	0.10
Mozambique	13248	27978	0.47	0.31	0.22	0.45	0.33	0.21	0.964	0.629	5.45	4.60
Myanmar	40626	53899	0.38	0.36	0.27	0.28	0.34	0.39	0.465	0.205	2.30	0.30
Nepal	18749	28511	0.42	0.32	0.25	0.33	0.36	0.32	0.299	0.132	2.32	0.10

Country	Population (1000s)		1990 age distributions (proportions)			2015 age distributions (proportions)			Mortality rates per 100 person years, 2015, age:		Fertility rates 2015 (lifetime births per woman)	Female (15-24) HIV % 2016
	1990	2015	0-14	15-34	≥35	0-14	15-34	≥35	0-14	15-34		
Netherlands	14965	16924	0.18	0.33	0.49	0.17	0.24	0.60	0.029	0.030	1.73	0.10
New Zealand	3398	4529	0.23	0.33	0.44	0.20	0.26	0.53	0.044	0.067	2.04	0.00
Nigeria	95270	182203	0.45	0.32	0.23	0.44	0.33	0.23	0.295	0.609	5.74	1.60
Norway	4247	5212	0.19	0.30	0.51	0.18	0.27	0.55	0.021	0.058	1.82	0.00
Pakistan	107678	188927	0.43	0.32	0.25	0.35	0.36	0.29	0.751	0.135	3.72	0.10
Philippines	61947	100700	0.41	0.36	0.24	0.32	0.35	0.33	0.252	0.155	3.05	0.10
Poland	37954	38267	0.25	0.30	0.45	0.15	0.28	0.57	0.046	0.072	1.33	0.00
Portugal	9953	10352	0.21	0.31	0.49	0.14	0.22	0.64	0.027	0.043	1.28	0.00
Romania	23489	19512	0.24	0.30	0.46	0.16	0.23	0.61	0.092	0.075	1.48	0.10
Russia	147558	143456	0.23	0.30	0.47	0.17	0.28	0.56	0.095	0.252	1.70	0.00
Saudi Arabia	16327	31557	0.42	0.37	0.22	0.26	0.34	0.40	0.149	0.078	2.72	0.10
Senegal	7556	15127	0.47	0.32	0.22	0.44	0.34	0.22	0.514	0.213	5.00	0.10
Serbia	9518	8850	0.24	0.29	0.47	0.16	0.26	0.58	0.069	0.061	1.59	0.10
Slovakia	5288	5426	0.25	0.31	0.44	0.15	0.28	0.57	0.049	0.066	1.39	0.10
Slovenia	2006	2068	0.21	0.31	0.49	0.15	0.23	0.62	0.430	0.081	1.58	0.10
Spain	39304	46122	0.20	0.32	0.48	0.15	0.21	0.64	0.029	0.035	1.33	0.10
Sweden	8567	9777	0.18	0.27	0.55	0.17	0.25	0.57	0.024	0.049	1.90	0.10
Switzerland	6675	8298	0.17	0.30	0.53	0.15	0.25	0.60	0.033	0.038	1.53	0.00
Syria	12446	18735	0.47	0.34	0.19	0.38	0.34	0.28	0.356	0.082	3.10	0.00
Taiwan	20312	23486	0.27	0.37	0.36	0.14	0.28	0.58	0.043	0.069	1.11	0.00
Tajikistan	5283	8483	0.44	0.33	0.23	0.35	0.37	0.28	0.481	0.101	3.50	0.10
Tanzania	25460	53471	0.46	0.33	0.21	0.45	0.33	0.22	0.521	0.315	5.24	2.30
Thailand	56582	67959	0.30	0.38	0.31	0.18	0.27	0.55	0.130	0.188	1.53	0.20
Tunisia	8233	11274	0.37	0.35	0.28	0.24	0.33	0.43	0.172	0.059	2.25	0.10
Turkey	53921	78271	0.36	0.35	0.30	0.26	0.33	0.42	0.178	0.125	2.12	0.00
Turkmenistan	3684	5563	0.41	0.36	0.24	0.30	0.36	0.34	0.484	0.151	3.00	0.00
UK	57179	64714	0.19	0.30	0.51	0.18	0.26	0.56	0.056	0.129	1.88	0.00
Ukraine	51462	44822	0.21	0.28	0.50	0.15	0.27	0.58	0.069	0.069	1.49	0.60
Uruguay	3110	3433	0.26	0.30	0.44	0.21	0.29	0.50	0.109	0.081	2.04	0.10
USA	252500	321774	0.22	0.32	0.46	0.19	0.27	0.54	0.055	0.083	1.88	0.00

Country	Population (1000s)		1990 age distributions (proportions)			2015 age distributions (proportions)			Mortality rates per 100 person years, 2015, age:		Fertility rates 2015 (lifetime births per woman)	Female (15-24) HIV % 2016
	1990	2015	0-14	15-34	≥35	0-14	15-34	≥35	0-14	15-34		
Uzbekistan	20461	29892	0.41	0.35	0.24	0.29	0.37	0.34	0.469	0.133	2.38	0.00
Viet Nam	68208	93448	0.37	0.36	0.26	0.23	0.35	0.42	0.207	0.116	1.96	0.10

* Taken from the UN Department of Economic and Social Affairs and the World Bank.

6.14. Data quality

Table 6.8 shows the data estimates for the HCV prevalence among the general population and PWID, and the estimates for the population percentage of PWID among adults. Also presented in table 6.8 are the estimate source, year, and the data quality grades taken from the literature. These data quality grades were available from Blach et al. 2017, Gower et al. 2014, Degenhardt et al. 2017, Grebely et al. 2018, and Mathers et al. 2008(40, 77, 124, 127, 245). The Blach and Gower papers used the same system to produce a grade for data quality, whilst the Degenhardt and Grebely papers used the same system as each other, and the Mathers paper used a similar system. These grading systems are described below briefly; the original papers describe them in more detail.

For HCV prevalence among the general population, Blach et al. 2017 and Gower et al. 2014 initially scored studies on a scale of 0-10, based on a combined score of the generalisability, sample size, and year of the analysis. The generalisability score (0-10) was assigned based on geographic scope and the population type. The sample size score (0-10) was the log of the sample size, capped at 10. The analysis year score was given as 6 for 2000-3, 8 for 2004-10, and 10 for those after 2010. The overall score was calculated as the sum of 0.6 multiplied by the generalisability score, 0.2 multiplied by the sample size score, and 0.2 multiplied by the year score. The 0-10 overall scores were then converted to produce a data quality scale of (lowest to highest) 1-3; where 0.0<4.0 became a score of 1, 4.0<8.0 became 2, and 8.0<10.0 became 3. Modelling studies were scored as 2, whilst studies without a formal assessment were given a score of 1.

For HCV prevalence among PWID, Degenhardt et al. 2017 and Grebely et al. 2018 assigned a grade from U to A (lowest to highest: U, D2, D1, C, B2, B1, A). Estimates were graded as follows: U – estimate with methodology unknown; D2 – self-report; D1 – registration or notification data; C – single-site seroprevalence study with one sample type (eg. treatment or outreach sample); B2 – single-site seroprevalence study with multiple sample types; B1 – multi-site seroprevalence study with one sample type; A – multi-site seroprevalence study with at least two sample types.

For data on the population percentage of PWID among adults, the Degenhardt and Grebely papers graded estimates (lowest to highest: D2, D1, C, B, A3, A2, A1) as follows: D2 – other

estimates with unknown methodology; D1 – official government estimate with methodology unknown; C – expert judgement with method by which estimate was obtained known; Delphi method or other consensus estimate; government registrations of drug users; B – general population household survey; A3 – network scale-up method; A2 – indirect prevalence estimation methods; A1 – multi-parameter evidence synthesis. Mathers et al. 2008, used the same method but for the estimate grade but grouped A3, A2, and A1 together as A.

For general population HCV prevalence, 14 (16%) country estimates were scored as 3, 34 (39%) were scored 2, and 28 (32%) were scored 1, whilst 12 (14%) country estimates did not come from reviews with scores. For PWID HCV prevalence estimates, 22 (25%) had at least one estimate of A (eg. if they were scored "A; B1" then A was taken), 48 (55%) had a grade of B (47 B1), and 16 (18%) were graded C or lower, whilst 2 (2%) countries did not have scores. For the proportion of the population that are PWID, 49 (56%) of country estimates were graded A, 5 (6%) were given B, and 14 (16%) were given a grade of C or lower. There were 14 (23%) countries that did not have graded estimates. Most ungraded estimates are from reviews with less clear methodology so would likely receive low scores.

Table 6.8: Country-level sampled ranges for antibody prevalence of HCV among the general population and PWID, as well as the population percentage of PWID among adults, and the estimate source, year, and grades*.

Country	Prevalence of HCV among general population				Prevalence of HCV among PWID				Population percentage of PWID			
	Estimate (Estimate range)	Year	Grade	Source	Estimate (Estimate range)	Year	Grade	Source	Estimate (Estimate range)	Year	Grade	Source
Afghanistan	1.10% (0.40%, 1.92%)	2007	2	(40)	37.8% (27.5%, 48.1%)	2012	A; B1; C	(77)	0.80% (0.50%, 1.09%)	2012	A2	(77)
Albania	3.00% (2.01%, 3.99%)	2008	NA	(160)	34.0% (27.5%, 41.0%)	2011	B1	(77)	0.42% (0.28%, 0.56%)	2008	NA	(160)
Argentina	1.50% (0.32%, 2.00%)	2007	1	(40)	54.6% (51.1%, 58.1%)	2001	B1	(77)	0.29% (0.29%, 0.30%)	1999	D1	(77)
Armenia	4.00% (2.68%, 5.32%)	2010	NA	(210)	42.7% (29.3%, 56.1%)	2012	B1	(77)	0.62% (0.41%, 1.35%)	2010	A2	(77)
Australia	1.30% (1.20%, 1.85%)	2012	2	(40)	53.5% (50.2%, 56.9%)	2014	B1	(77)	0.60% (0.43%, 0.76%)	2016	A	(77)
Austria	0.50% (0.10%, 0.70%)	2008	1	(40)	60.9% (54.8%, 67.0%)	2012	A; B1: C	(77)	0.32% (0.22%, 0.42%)	2000	A	(77)
Azerbaijan	3.70% (2.48%, 4.92%)	2010	2	(40)	62.1% (47.1%, 77.2%)	2012	B2	(77)	0.61% (0.49%, 0.74%)	2011	A2	(77)
Bangladesh	1.26% (0.20%, 2.23%)	2010	1	(124)	33.9% (22.4%, 45.4%)	2013	A; C	(77)	0.07% (0.06%, 0.07%)	2016	A2	(77)
Belarus	1.26% (0.86%, 2.85%)	2006	1	(124)	58.3% (43.3%, 73.3%)	2015	B1	(77)	0.59% (0.22%, 0.96%)	2015	A2	(77)
Belgium	0.87% (0.12%, 1.10%)	1994	1	(40)	58.4% (47.0%, 69.7%)	2014	B1; C	(77)	0.35% (0.24%, 0.49%)	2014	A2	(77)
Bosnia	0.10% (0.07%, 0.13%)	2008	NA	(160)	39.9% (27.5%, 52.4%)	2014	B1; C	(77)	0.17% (0.11%, 0.23%)	2008	NA	(160)
Brazil	1.38% (1.12%, 1.64%)	2007	3	(40)	63.9% (60.5%, 67.3%)	2001	B1	(77)	0.67% (0.51%, 0.87%)	2003	D1	(77)
Bulgaria	1.50% (0.70%, 2.43%)	2012	1	(40)	68.7% (64.3%, 73.0%)	2014	A	(77)	0.38% (0.30%, 0.45%)	2005	A	(77)
Canada	0.96% (0.61%, 1.34%)	2011	2	(40)	70.6% (60.1%, 93.9%)	2014	A; B1	(77)	0.39% (0.31%, 0.47%)	2004	B	(127)
China	1.21% (0.93%, 1.49%)	2015	2	(40)	43.1% (27.5%, 58.6%)	2015	A; B1; C	(77)	0.25% (0.19%, 0.31%)	2005	A	(77)
Croatia	0.90% (0.50%, 1.40%)	2011	2	(40)	36.7% (28.1%, 45.3%)	2015	B1	(77)	0.23% (0.18%, 0.29%)	2015	A2	(77)
Cyprus	0.56% (0.45%, 1.87%)	2001	1	(124)	49.7% (44.4%, 55.0%)	2014	A; B1	(77)	0.08% (0.04%, 0.12%)	2014	A2	(77)
Czech Republic	0.57% (0.20%, 0.70%)	2012	1	(40)	18.3% (14.5%, 22.1%)	2015	B1	(77)	0.64% (0.61%, 0.67%)	2014	A2	(77)
Denmark	0.63% (0.48%, 0.72%)	2007	2	(40)	42.6% (36.1%, 49.1%)	2011	B1	(77)	0.45% (0.35%, 0.52%)	2009	A2	(77)
Egypt	10.00% (9.50%, 10.50%)	2015	3	(181)	49.4% (35.8%, 63.0%)	1995	C	(77)	0.21% (0.13%, 0.28%)	2005	NA	(258)
Estonia	1.97% (1.50%, 2.00%)	2013	1	(40)	79.2% (67.4%, 91.0%)	2014	B1; C	(77)	0.94% (0.69%, 1.73%)	2009	A2	(77)
Finland	0.68% (0.60%, 0.90%)	2013	1	(124)	73.7% (69.9%, 77.2%)	2014	B1	(77)	0.46% (0.41%, 0.67%)	2012	D2	(77)
France	0.84% (0.45%, 1.10%)	2004	3	(249)	64.0% (60.8%, 67.0%)	2011	A	(77)	0.20% (0.16%, 0.23%)	2011	D2	(77)
FYROM	0.50% (0.34%, 0.67%)	2008	NA	(160)	62.2% (59.4%, 64.9%)	2013	B1	(77)	0.16% (0.11%, 0.21%)	2008	NA	(160)

Country	Prevalence of HCV among general population				Prevalence of HCV among PWID				Population percentage of PWID			
	Estimate (Estimate range)	Year	Grade	Source	Estimate (Estimate range)	Year	Grade	Source	Estimate (Estimate range)	Year	Grade	Source
Georgia	5.40% (4.51%, 6.32%)	2015	3	(132)	69.1% (58.0%, 80.2%)	2015	B1; C	(77)	4.19% (0.48%, 7.90%)	2004	C	(77)
Germany	0.58% (0.30%, 0.90%)	2012	1	(40)	65.0% (60.6%, 69.4%)	2014	B1	(77)	0.24% (0.03%, 0.45%)	2000	A	(77)
Ghana	2.10% (1.20%, 5.50%)	2014	2	(40)	40.1% (34.8%, 45.4%)	2005	B1	(77)	0.05% (0.03%, 0.07%)	2008	NA	(304)
Greece	1.79% (0.50%, 2.61%)	2011	3	(40)	65.7% (61.8%, 69.5%)	2014	A	(77)	0.07% (0.06%, 0.09%)	2014	A2	(77)
Hungary	0.70% (0.40%, 2.70%)	2014	1	(40)	46.4% (30.4%, 62.8%)	2015	A	(77)	0.06% (0.03%, 0.08%)	2005	A	(77)
Iceland	0.41% (0.33%, 0.48%)	2013	2	(40)	63.0% (59.8%, 66.2%)	1993	C	(77)	0.24% (0.16%, 0.32%)	2008	NA	(160)
India	0.84% (0.50%, 1.50%)	2013	1	(40)	40.0% (33.9%, 46.1%)	2015	B1; C	(77)	0.02% (0.01%, 0.03%)	2006	A	(77)
Indonesia	0.80% (0.10%, 1.70%)	2007	3	(40)	89.2% (85.3%, 92.3%)	2015	C	(77)	0.11% (0.09%, 0.13%)	2012	A2	(77)
Iran	0.50% (0.20%, 1.00%)	2006	2	(40)	44.1% (28.2%, 59.9%)	2014	C; B1; A	(77)	0.28% (0.19%, 0.37%)	2013	A3	(77)
Ireland	0.70% (0.67%, 1.60%)	2010	2	(40)	74.6% (72.3%, 76.9%)	2003	C	(77)	0.27% (0.20%, 0.33%)	1996	A	(77)
Israel	1.96% (0.90%, 2.10%)	2006	2	(40)	45.3% (38.1%, 52.6%)	2010	C	(77)	0.41% (0.27%, 0.55%)	2008	NA	(160)
Italy	2.43% (1.60%, 7.30%)	2001	1	(40)	57.9% (52.5%, 63.3%)	2014	B1; C	(77)	0.83% (0.57%, 1.14%)	1996	A	(77)
Japan	0.98% (0.49%, 2.20%)	2011	2	(40)	64.8% (55.0%, 74.5%)	1994	C	(77)	0.47% (0.36%, 0.58%)	2004	D1	(77)
Kazakhstan	3.20% (1.30%, 4.26%)	2010	2	(40)	58.8% (54.0%, 63.6%)	2005	C	(77)	0.96% (0.64%, 1.42%)	2006	A	(77)
Kenya	0.76% (0.20%, 1.01%)	2007	2	(40)	16.4% (10.9%, 23.3%)	2013	C	(77)	0.12% (0.03%, 0.20%)	2012	A2	(77)
Kyrgyzstan	2.45% (1.60%, 6.70%)	2010	1	(124)	43.9% (40.6%, 47.2%)	2013	B1	(77)	0.74% (0.50%, 1.11%)	2006	A	(77)
Latvia	2.40% (1.70%, 3.30%)	2008	2	(40)	74.4% (67.6%, 81.2%)	2014	B1	(77)	0.92% (0.73%, 1.17%)	2012	A2	(77)
Lebanon	0.21% (0.11%, 0.70%)	2011	2	(40)	23.4% (15.3%, 33.3%)	2013	C	(77)	0.14% (0.09%, 0.19%)	2005	NA	(258)
Libya	1.20% (1.10%, 1.30%)	2005	3	(40)	94.5% (91.5%, 96.7%)	2010	B1	(77)	0.05% (0.01%, 0.10%)	2001	C	(77)
Lithuania	1.96% (1.21%, 2.71%)	2010	2	(40)	41.1% (38.1%, 44.2%)	2014	B1; C	(77)	0.22% (0.12%, 0.34%)	2006	C	(77)
Luxembourg	1.34% (0.56%, 1.61%)	2006	1	(40)	81.3% (76.2%, 85.8%)	2005	A	(77)	0.57% (0.45%, 0.69%)	2009	A1	(77)
Madagascar	1.20% (0.75%, 1.72%)	2004	2	(40)	5.5% (2.1%, 9.0%)	2012	B1	(77)	0.12% (0.02%, 0.59%)	2014	A2	(77)
Malaysia	1.90% (0.30%, 7.70%)	2011	2	(40)	67.1% (62.9%, 71.1%)	2007	B1	(77)	1.33% (1.11%, 1.56%)	2002	C	(77)
Malta	0.36% (0.26%, 0.60%)	2010	1	(40)	25.2% (13.1%, 37.3%)	2014	A	(77)	0.26% (0.17%, 0.35%)	2008	NA	(160)
Mauritius	2.10% (1.41%, 2.79%)	2010	NA	(210)	97.1% (96.0%, 98.1%)	2011	B1	(77)	0.78% (0.39%, 1.54%)	2014	B1	(77)
Mexico	1.40% (1.10%, 1.60%)	2000	3	(40)	95.3% (93.3%, 97.3%)	2005	A	(77)	0.18% (0.12%, 0.25%)	2011	B	(77)
Moldova	4.46% (2.30%, 4.46%)	2010	1	(124)	50.1% (34.1%, 66.1%)	2013	B2	(77)	0.40% (0.25%, 0.54%)	2008	A3	(77)

Country	Prevalence of HCV among general population				Prevalence of HCV among PWID				Population percentage of PWID			
	Estimate (Estimate range)	Year	Grade	Source	Estimate (Estimate range)	Year	Grade	Source	Estimate (Estimate range)	Year	Grade	Source
Montenegro	1.20% (0.80%, 1.60%)	2008	NA	(160)	43.4% (39.8%, 47.1%)	2008	B1	(77)	0.40% (0.27%, 0.53%)	2008	NA	(160)
Morocco	1.20% (1.10%, 1.93%)	2008	2	(40)	53.9% (33.7%, 74.0%)	2013	B1	(77)	0.13% (0.07%, 0.20%)	2013	A2; B	(77)
Mozambique	1.30% (0.10%, 6.90%)	2011	NA	(309)	67.1% (62.9%, 71.2%)	2014	B1	(77)	0.20% (0.00%, 0.41%)	2014	A1; A2	(77)
Myanmar	1.69% (0.95%, 2.66%)	2009	1	(124)	29.5% (26.9%, 32.2%)	2010	B1; C	(77)	0.48% (0.32%, 0.65%)	2014	A2	(77)
Nepal	0.64% (0.43%, 0.85%)	2010	NA	(210)	44.5% (30.8%, 58.2%)	2015	B1	(77)	0.20% (0.19%, 0.21%)	2011	A2	(77)
Netherlands	0.22% (0.07%, 0.37%)	2009	2	(40)	55.3% (49.7%, 60.9%)	2014	A; B1	(77)	0.03% (0.02%, 0.04%)	2001	A	(77)
New Zealand	1.43% (0.81%, 2.15%)	2013	1	(40)	71.9% (63.2%, 80.6%)	2015	B1	(77)	0.73% (0.49%, 0.97%)	2006	B	(77)
Nigeria	2.20% (2.10%, 2.50%)	2012	2	(40)	5.8% (3.5%, 8.9%)	2010	C	(77)	0.35% (0.23%, 0.47%)	2008	NA	(304)
Norway	0.55% (0.45%, 0.70%)	2012	1	(40)	64.8% (60.4%, 69.1%)	2012	A	(77)	0.24% (0.21%, 0.29%)	2013	A2	(77)
Pakistan	4.80% (4.70%, 5.10%)	2008	3	(40)	36.5% (5.1%, 79.1%)	2013	C; B1; A	(77)	0.37% (0.32%, 0.42%)	2011	A3	(77)
Philippines	0.94% (0.33%, 2.00%)	2003	2	(40)	35.2% (15.9%, 54.5%)	2011	B1	(77)	0.04% (0.03%, 0.05%)	2011	C	(77)
Poland	0.86% (0.59%, 1.14%)	2009	2	(40)	58.7% (55.1%, 66.2%)	2005	A	(77)	0.27% (0.18%, 0.36%)	2008	NA	(160)
Portugal	1.50% (0.47%, 2.87%)	1995	1	(40)	87.7% (80.5%, 95.0%)	2016	B1	(77)	0.22% (0.19%, 0.25%)	2012	D2	(77)
Romania	3.23% (2.94%, 3.55%)	2007	3	(40)	83.8% (80.6%, 87.1%)	2009	B1; C	(77)	0.62% (0.46%, 0.84%)	2014	A2	(77)
Russia	4.10% (1.16%, 5.60%)	2010	2	(40)	68.7% (59.6%, 77.9%)	2012	B1; B2	(77)	1.78% (0.94%, 2.71%)	2007	D1	(77)
Saudi Arabia	0.51% (0.41%, 0.61%)	2011	1	(40)	77.8% (73.2%, 81.9%)	2012	C	(77)	0.20% (0.13%, 0.27%)	2005	NA	(258)
Senegal	1.00% (0.00%, 4.60%)	2009	NA	(309)	39.3% (31.1%, 47.9%)	2011	B1	(77)	0.08% (0.05%, 0.11%)	2008	NA	(304)
Serbia	0.50% (0.34%, 0.67%)	2008	NA	(160)	25.9% (22.1%, 29.7%)	2014	B1	(77)	0.49% (0.41%, 0.58%)	2016	A2	(77)
Slovakia	1.40% (0.88%, 1.98%)	2011	3	(40)	56.1% (35.6%, 76.7%)	2014	B1; C	(77)	0.49% (0.35%, 0.89%)	2006	A	(77)
Slovenia	0.40% (0.30%, 0.50%)	2015	1	(40)	30.5% (26.4%, 34.5%)	2014	B1	(77)	0.42% (0.30%, 0.55%)	2012	C	(77)
Spain	1.50% (0.40%, 2.64%)	2012	2	(40)	71.0% (69.5%, 72.5%)	2012	B1	(77)	0.08% (0.05%, 0.10%)	2011	NA	(97)
Sweden	0.56% (0.47%, 0.69%)	2012	2	(40)	81.7% (79.6%, 83.6%)	2014	C	(77)	0.13% (0.03%, 0.62%)	2011	A2	(77)
Switzerland	1.55% (0.80%, 1.75%)	1998	2	(40)	74.6% (69.3%, 79.4%)	2014	B1	(77)	0.24% (0.19%, 0.29%)	2006	A2	(77)
Syria	2.80% (0.60%, 3.72%)	2004	3	(40)	60.5% (40.5%, 80.5%)	1999	C	(268)	0.07% (0.04%, 0.09%)	2005	NA	(258)
Taiwan	3.28% (2.50%, 8.60%)	2000	2	(40)	91.0% (89.5%, 92.4%)	2011	C	(77)	0.30% (0.20%, 0.40%)	2005	NA	(3)
Tajikistan	3.06% (1.10%, 6.70%)	2010	1	(124)	61.3% (56.8%, 65.6%)	2004	B1	(77)	0.45% (0.30%, 0.66%)	2006	A	(77)
Tanzania	2.70% (0.20%, 7.80%)	2013	NA	(309)	27.7% (22.4%, 33.5%)	2011	A	(77)	1.24% (0.72%, 1.76%)	2012	A2	(77)

Country	Prevalence of HCV among general population				Prevalence of HCV among PWID				Population percentage of PWID			
	Estimate (Estimate range)	Year	Grade	Source	Estimate (Estimate range)	Year	Grade	Source	Estimate (Estimate range)	Year	Grade	Source
Thailand	0.94% (0.75%, 3.66%)	2014	2	(40)	88.5% (82.6%, 92.9%)	2005	C	(77)	0.11% (0.03%, 0.18%)	2013	A3	(77)
Tunisia	1.27% (0.20%, 1.70%)	1996	2	(40)	29.1% (25.7%, 32.6%)	2009	B1	(77)	0.21% (0.14%, 0.29%)	2005	NA	(258)
Turkey	0.95% (0.60%, 2.10%)	2009	3	(40)	44.9% (41.7%, 48.2%)	2015	B1	(77)	0.42% (0.28%, 0.56%)	2008	NA	(160)
Turkmenistan	5.55% (1.10%, 6.70%)	2010	1	(124)	60.6% (46.2%, 75.0%)	2005	NA	(3)	0.40% (0.27%, 0.53%)	2008	NA	(160)
UK	0.50% (0.40%, 0.75%)	2005	2	(40)	46.0% (36.8%, 55.2%)	2008	NA	(160)	0.39% (0.38%, 0.42%)	2005	A	(245)
Ukraine	3.58% (0.86%, 4.46%)	2010	1	(124)	53.9% (49.2%, 58.7%)	2015	B1	(77)	0.97% (0.52%, 1.79%)	2012	A2	(77)
Uruguay	1.00% (0.67%, 1.33%)	2010	NA	(210)	21.9% (19.0%, 24.8%)	2003	C	(77)	0.30% (0.10%, 0.87%)	2007	B	(77)
USA	1.30% (1.20%, 1.50%)	2007	3	(78)	53.1% (38.1%, 68.0%)	2016	C; B2; A	(77)	1.40% (0.57%, 1.88%)	2007	A2	(77)
Uzbekistan	13.10% (6.40%, 13.11%)	2000	2	(40)	51.7% (46.8%, 56.6%)	2001	A	(77)	0.47% (0.32%, 0.70%)	2006	A	(77)
Viet Nam	1.49% (1.20%, 2.00%)	2012	1	(40)	58.3% (42.7%, 74.0%)	2014	A; B1	(77)	0.25% (0.19%, 0.31%)	2005	D1	(77)

NA: Not available

Prevalence ranges are taken from the literature, and where they were not available ranges of ±33% are used.

* Countries listed in green have moderate to good quality data estimates for all of the prevalence of HCV among the general population (graded as 2 or above), the prevalence of HCV among PWID (graded as B or above), and the population percentage of adults that are PWID (graded as B or above), whilst countries listed in orange have two of these estimates graded as moderate to good quality, and countries listed in red have one or less.

Table 6.9: Country-level injecting durations taken from Degenhardt et al(77)†.

Country	Injecting drug use duration, years (Range†)
Afghanistan	6.8 (3.4, 13.6)
Albania	12.4 (6.2, 24.8)*
Argentina	13.2 (6.6, 26.4)*
Armenia	11.8 (5.9, 23.6)*
Australia	15.4 (7.7, 30.8)
Austria	13.0 (6.5, 26.0)
Azerbaijan	8.8 (4.4, 17.6)
Bangladesh	6.0 (3.0, 12.0)
Belarus	10.9 (5.5, 21.8)
Belgium	13.3 (6.7, 26.6)
Bosnia	15.0 (7.5, 30.0)
Brazil	13.2 (6.6, 26.4)*
Bulgaria	9.0 (4.5, 18.0)
Canada	14.3 (7.2, 28.6)
China	7.1 (3.6, 14.2)
Croatia	13.5 (6.8, 27.0)
Cyprus	8.8 (4.4, 17.6)
Czech Republic	11.8 (5.9, 23.6)*
Denmark	18.2 (9.1, 36.4)
Egypt	5.2 (2.6, 10.4)*
Estonia	8.1 (4.1, 16.2)
Finland	12.4 (6.2, 24.8)*
France	12.4 (6.2, 24.8)*
FYROM	12.4 (6.2, 24.8)*
Georgia	14.1 (7.1, 28.2)
Germany	13.9 (7.0, 27.8)
Ghana	10.0 (5.0, 20.0)
Greece	11.7 (5.9, 23.4)
Hungary	9.6 (4.8, 19.2)
Iceland	7.0 (3.5, 14.0)
India	7.2 (3.6, 14.4)
Indonesia	7.1 (3.6, 14.2)
Iran	8.2 (4.1, 16.4)
Ireland	12.4 (6.2, 24.8)*
Israel	14.0 (7.0, 28.0)
Italy	9.0 (4.5, 18.0)
Japan	7.3 (3.7, 14.6)*
Kazakhstan	5.0 (2.5, 10.0)
Kenya	5.3 (2.7, 10.6)
Kyrgyzstan	6.3 (3.2, 12.6)
Latvia	9.1 (4.6, 18.2)
Lebanon	5.2 (2.6, 10.4)*
Libya	5.2 (2.6, 10.4)*
Lithuania	10.0 (5.0, 20.0)
Luxembourg	12.4 (6.2, 24.8)*
Madagascar	7.8 (3.9, 15.6)*

Country	Injecting drug use duration, years (Range†)
Malaysia	13.9 (7.0, 27.8)
Malta	12.4 (6.2, 24.8)*
Mauritius	14.0 (7.0, 28.0)
Mexico	16.1 (8.1, 32.2)
Moldova	12.7 (6.4, 25.4)
Montenegro	6.0 (3.0, 12.0)
Morocco	10.0 (5.0, 20.0)
Mozambique	7.8 (3.9, 15.6)*
Myanmar	3.4 (1.7, 6.8)
Nepal	5.2 (2.6, 10.4)
Netherlands	12.4 (6.2, 24.8)*
New Zealand	15.4 (7.7, 30.8)*
Nigeria	8.0 (4.0, 16.0)
Norway	14.0 (7.0, 28.0)
Pakistan	5.1 (2.6, 10.2)
Philippines	6.8 (3.4, 13.6)
Poland	14.4 (7.2, 28.8)
Portugal	12.4 (6.2, 24.8)*
Romania	9.8 (4.9, 19.6)
Russia	7.6 (3.8, 15.2)
Saudi Arabia	5.2 (2.6, 10.4)*
Senegal	7.8 (3.9, 15.6)*
Serbia	8.8 (4.4, 17.6)
Slovakia	11.8 (5.9, 23.6)
Slovenia	12.4 (6.2, 24.8)*
Spain	11.2 (5.6, 22.4)
Sweden	21.0 (10.5, 42.0)
Switzerland	12.4 (6.2, 24.8)*
Syria	5.2 (2.6, 10.4)*
Taiwan	15.5 (7.8, 31.0)
Tajikistan	5.9 (3.0, 11.8)
Tanzania	4.3 (2.2, 8.6)
Thailand	7.3 (3.7, 14.6)*
Tunisia	5.2 (2.6, 10.4)*
Turkey	4.0 (2.0, 8.0)
Turkmenistan	5.9 (3.0, 11.8)*
UK	10.0 (5.0, 20.0)
Ukraine	12.2 (6.1, 24.4)
Uruguay	13.2 (6.6, 26.4)*
USA	16.2 (8.1, 32.4)
Uzbekistan	5.9 (3.0, 11.8)*
Viet Nam	5.8 (2.9, 11.6)

† Ranges for injecting duration are taken as 50% and 200% of the estimate for the current duration of injecting.

* Countries for which the regional estimates of injecting duration were used.

6.15. Historical treatment numbers

Historical annual treatment numbers were included, where available, for the years 2004 to 2017. Data from the Centre for Disease Analysis (CDA) covering 2004-2016 were used for China and Taiwan and the 2016 estimates were extended to 2017(54). Treatment numbers for 2014-2017 were also taken from WHO access to treatment reports where available(400, 409). The data underlying a paper by Hill et al. on the treatment numbers for 2015-2017 were also made available to me(157). To obtain the treatment numbers for the years prior to this, firstly data were taken from the series of Journal of Viral Hepatitis papers on the Historical Epidemiology of hepatitis C virus in selected countries(49, 217, 223, 319). Estimates from these papers were available for one year. For the 48 countries that had estimates from these papers, the estimates of treatment numbers (e.g. for 2011) were extended to cover the time span of 2004-2017 (where data were not available for the later years). 2004 was chosen as the earliest year of treatment to coincide with the earliest estimates available from the CDA.

Additionally, to increase the information available on treatment numbers, for each country in the model two Google searches were performed (Google was chosen over Pubmed or Web of Science to give a broader range of source types), the first with the words "HCV treated DAA" and the country name, and the second with "hepatitis c treatment" and the country name. Estimates were included if there was evidence of treatment in the countries not included in the Journal of Viral Hepatitis series. Multiple sources could be used for each country to cover the different years. Sources could include government treatment databases, news briefings, published papers, posters, presentations, reports, and white papers. For some posters and presentations, visual estimates had to be made as the exact figures were not available. More information on the sources of information for annual treatment numbers are available in table 6.10.

To improve the treatment number estimates over time, the Journal of Viral Hepatitis series estimates that had been extended to cover multiple years were then overwritten if other information on treatment numbers was available from these other sources. Any previous estimate (from any of the sources listed in the paragraph above) not from the Journal of Viral Hepatitis series was carried forward across subsequent years or any later estimate was carried backwards, whichever number was lower. For example, Finland had an estimate of 100 annual treatments in 2004(300), and 200 in 2010(300) so 100 was used for 2005-2009 and

200 from 2010 onwards. Another example is Belgium, which had an estimate of 900 annual treatments in 2004(300) and 710 in 2010(49, 300, 348), so 710 was used for 2005-2009 and was also carried forwards until 2014, as an updated estimate of 1300 was available in 2015(154). More generally, 2016 estimates were extended to 2017 if no other information was available.

Absolute treatment numbers are converted to rates to be input into the model by dividing with the total number of infected individuals as the denominator. Although these treatment numbers are not varied, the treatment rates vary due to changes in other parameters. Due to a lack of information for treatment numbers in particular subgroups, eg. PWID or those with cirrhosis, treatment was spread throughout different subgroups proportional to the number of infections in each group. However, this assumption was investigated in a sensitivity analysis where the treatment rates among PWID were halved and among people with cirrhosis were doubled, discussed in sections 7.2.2 and 8.2.3.

Table 6.10: Historical HCV treatment numbers 2004-2017.

	Treatments per year														
Country	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Sources**
Afghanistan	0	0	0	0	0	0	0	0	0	0	0	1	10	10	(157)
Albania	0	0	0	0	0	0	0	0	0	117	117	117	48	48	(32)
Argentina	200	200	200	200	200	200	200	200	200	200	350	200	1204	1204	(157, 307, 319)
Armenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Australia	2245	2134	3215	3800	3650	3800	3750	3050	2726	3540	2800	7300	40000	30000	(137, 157, 409)
Austria	1200	1100	1100	1100	1100	1100	1100	1100	1100	1100	1100	2000	1500	1500	(49, 154, 157, 300)
Azerbaijan	0	0	0	0	0	0	0	0	0	0	0	210	210	210	(157)
Bangladesh	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Belarus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Belgium	900	710	710	710	710	710	710	710	710	710	710	1300	1080	1080	(49, 154, 157, 300, 348)
Bosnia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Brazil	10000	10000	10000	10000	10000	10000	10000	11700	7500	7500	7500	7500	41000	45016	(42, 49, 157, 409)
Bulgaria	346	346	346	346	346	346	346	400	380	377	549	611	350	350	(157, 334)
Canada	4800	4800	4800	4800	4800	4800	4800	4800	4800	4800	4800	14200	9500	9500	(49, 157)
China	5000	13636	22273	30909	39545	48182	56818	65455	74091	82727	91364	100000	100000	100000	(54, 157)
Croatia	300	300	300	300	300	300	300	300	150	150	150	150	150	150	(154, 157, 223)
Cyprus	0	0	0	0	0	0	0	0	0	0	0	46	46	46	(154)
Czechia	800	800	800	800	800	800	900	880	880	880	880	880	910	910	(49, 154, 157, 300)
Denmark	100	100	100	100	100	100	200	100	100	100	344	630	511	511	(49, 154, 157, 300, 341)
Egypt	0	0	0	65000	65000	65000	65000	65000	30000	30000	30000	170000	700000	600000	(49, 55, 91, 400, 409)
Estonia	500	500	500	500	500	500	500	500	500	500	500	450	908	908	(154, 157, 217)
Finland	100	100	100	100	100	100	200	300	300	300	300	300	300	300	(154, 157, 300, 319)
France	14000	13287	13287	13287	12269	11332	9935	10325	12488	8382	11630	15189	16000	19300	(48, 55, 300)
FYROM	0	0	0	0	0	0	0	0	0	0	0	0	76	76	(170)
Georgia	0	0	0	0	0	0	0	0	0	0	0	6000	21500	15400	(55, 263)
Germany	8500	8500	8500	8500	8500	8500	9900	11667	11667	11667	7000	20100	13200	13000	(300, 310)

Country	Treatments per year 2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Sources
Ghana	20	20	20	20	20	20	20	20	20	20	20	20	20	20	(157, 223)
Greece	1970	1970	1970	1970	1970	1970	3000	1970	1970	1970	1970	2100	900	1134	(154, 157, 300, 319, 353)
Hungary	600	600	600	600	600	600	1200	1200	1200	1200	1200	1200	1477	1477	(154, 157, 217, 300)
Iceland	30	30	30	30	30	30	30	30	30	30	30	40	450	200	(55, 157, 319)
India	15000	15000	15000	15000	15000	15000	15000	15000	15000	15000	15000	42000	115000	115000	(157, 319, 400)
Indonesia	230	230	230	230	230	230	230	230	230	230	230	230	600	600	(157, 217, 257)
Iran	4500	4500	4500	4500	4500	4500	4500	4500	4500	4500	4500	4500	6000	6000	(157, 217)
Ireland	100	100	100	100	100	100	200	400	400	400	400	840	840	840	(154, 157, 300, 319)
Israel	1010	1010	1010	1010	1010	1010	1010	1010	1010	1010	1010	1500	1500	1500	(157, 319)
Italy	22000	12500	12500	12500	12500	12500	12500	12500	12500	12500	12500	35000	30000	43000	(4, 55, 300)
Japan	26900	26900	26900	26900	26900	26900	26900	26900	26900	26900	26900	26900	87900	38000	(55, 157, 217)
Kazakhstan	1800	1800	1800	1800	1800	1800	1800	1800	1800	1800	1400	1400	1132	1750	(157, 223, 229)
Kenya	0	0	0	0	0	0	0	0	0	0	0	0	0	6	(157)
Kyrgyzstan	0	0	0	0	0	0	0	0	0	0	0	0	100	100	(201)
Latvia	840	840	840	840	840	840	862	840	840	840	840	910	1071	1071	(25, 154, 157, 217)
Lebanon	170	170	170	170	170	170	170	170	170	170	170	170	325	325	(157, 217)
Libya	0	0	0	0	0	0	0	0	0	0	0	290	288	288	(157)
Lithuania	450	450	450	450	450	450	450	450	450	450	890	550	936	1518	(157, 174, 217)
Luxembourg	100	100	100	100	100	100	100	100	100	100	100	168	280	300	(21, 157, 319)
Madagascar	0	0	0	0	0	0	0	0	0	0	0	0	3	3	(157)
Malaysia	540	540	540	540	540	540	540	540	540	540	540	550	550	550	(157, 223)
Malta	0	0	0	0	0	0	0	0	0	0	0	12	70	70	(154, 157)
Mauritius	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Mexico	3100	3100	3100	3100	3100	3100	3100	3100	3100	3100	3100	3800	480	480	(157, 319)
Moldova	0	0	0	0	0	0	0	0	0	0	0	300	300	300	(229)
Montenegro	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Morocco	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000	100	6500	8000	(157, 400, 409)

Country	Treatments per year														Sources
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Mozambique	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Myanmar	0	0	0	0	0	0	0	0	0	0	0	0	0	2000	(206)
Nepal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Netherlands	900	900	900	900	900	900	1100	900	880	880	880	2000	2000	1200	(55, 154, 300, 319, 392)
New Zealand	900	900	900	900	900	900	900	900	900	900	900	1100	1882	1882	(157, 319)
Nigeria	300	300	300	300	300	300	300	300	300	300	300	300	300	300	(157, 223)
Norway	300	300	300	300	300	300	400	600	600	600	600	1100	1000	1000	(157, 300, 319)
Pakistan	0	23000	23000	23000	23000	23000	23000	55000	55000	55000	55000	65000	161000	161000	(157, 218, 409)
Philippines	0	0	0	0	0	0	0	0	0	0	0	550	550	550	(157)
Poland	1000	1000	1000	1000	1000	1000	2500	2100	2100	2100	2100	4000	5800	5800	(154, 157, 300, 319)
Portugal	200	200	200	200	200	200	2000	1200	1200	1200	1200	5449	8248	4836	(49, 67, 157, 300, 400)
Romania	2500	2500	2500	2500	2500	2500	6000	4100	4100	4100	4100	3400	6000	8131	(154, 157, 217, 300, 409)
Russia	500	500	500	500	500	500	6000	5500	5500	5500	8800	5500	8792	5500	(157, 201, 229, 300, 319)
Saudi Arabia	1900	1900	1900	1900	1900	1900	1900	1900	380	380	380	7500	2800	2800	(14, 157, 217)
Senegal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Serbia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Slovakia	200	200	200	200	200	200	500	300	300	300	300	350	316	316	(154, 157, 300, 319)
Slovenia	150	150	150	150	150	150	150	150	150	150	150	150	200	200	(154, 157, 217)
Spain	8000	8000	8000	8000	8000	8000	9800	9800	9800	9800	9800	38000	32000	29700	(49, 55, 154, 300)
Sweden	1500	1500	1500	1500	1500	1500	2000	1100	1100	1100	1130	2300	2500	2500	(49, 84, 154, 157, 300)
Switzerland	800	800	800	800	800	800	1100	1100	1100	1100	1100	1100	2300	3200	(49, 55, 300)
Syria	0	0	0	0	0	0	0	0	0	0	0	0	10	10	(157)
Taiwan	3549	4154	4967	5567	5117	5490	13515	11262	10586	9000	8000	8000	4000	4000	(54, 157)
Tajikistan	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Tanzania	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Thailand	0	0	0	0	0	0	0	0	0	0	0	920	3000	3000	(157)
Tunisia	0	0	0	0	0	0	0	0	0	0	0	1	1000	1000	(157)

Country	Treatments per year 2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Sources
Turkey	4170	4170	4170	4170	4170	4170	4170	4170	4170	4170	4170	4170	194	194	(157, 273)
Turkmenistan	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
UK	2500	2500	3000	4468	5091	5904	6449	6202	4000	4000	4000	9000	12000	14800	(55, 148, 154, 300, 409)
Ukraine	0	0	0	0	0	0	0	0	0	0	1100	2000	2500	1750	(157, 229, 409)
Uruguay	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
USA	0	125000	105000	80000	75000	70000	60000	72500	57500	30000	140000	260000	231000	231000	(50, 157)
Uzbekistan	0	0	0	0	0	0	0	0	0	0	0	1500	1500	1500	(157)
Viet Nam	0	0	0	0	0	0	0	0	0	0	0	0	4500	4500	(400)

CHAPTER 7. THE CONTRIBUTION OF INJECTING DRUG USE FOR HEPATITIS C VIRUS TRANSMISSION GLOBALLY, REGIONALLY, AND AT COUNTRY-LEVEL: A MODELLING STUDY

The work in this chapter was done in collaboration with Hannah Fraser, Aaron G Lim, Amy Peacock, Samantha Colledge, Josephine G Walker, Janni Leung, Jason Grebely, Sarah Larney, Natasha K Martin, Matthew Hickman, Louisa Degenhardt, Margaret T May, and Peter Vickerman, and is published in the Lancet Gastroenterology and Hepatology(371).

7.1. Introduction

Injecting drug use (IDU) is an important risk factor for the transmission of bloodborne viruses, due to sharing of used needles and injecting equipment(77). Although hepatitis C virus (HCV) prevalence amongst people who inject drugs (PWID) is generally high (>30%)(77), the prevalence of IDU in most countries is low (<1% of adults)(77). It is therefore generally assumed that IDU is usually only an important contributor to HCV transmission in low prevalence settings, mainly high-income countries (HICs) in Europe, Australasia, and North America(16). Conversely, its role in low and middle-income countries (LMICs), some of which have higher HCV prevalence(40), is thought to be small(327). In these settings, it is assumed that transmission is driven by other risk factors, such as unsterile medical injections, other medical procedures, unscreened blood transfusions, and community risks (e.g. barbering, tattooing, and body piercings)(16, 327, 367).

This role of different risk factors to HCV transmission in LMICs was discussed in relation to Pakistan in chapter 4 and Punjab, India, in chapter 5. Both settings had medical factors that were associated with prevalent infection and Pakistan also had community factors. In Punjab there is some evidence that IDU is a growing source of HCV transmission(326). However, the analysis in chapter 5 cannot truly quantify the role of IDU to HCV transmission as it is a cross sectional survey and focuses only on one state in Northern India.

Additionally, due to the survey sampling from households, PWID are likely to be under-represented. Two recent analyses attempted to quantify the role of IDU to the transmission and disease burden of HCV globally(76, 127). These estimated two very distinct measures; the proportion of global prevalent HCV infections that are amongst people who have recently injected drugs, around 8.5%(127), and the proportion of the global HCV morbidity burden attributable to IDU, roughly 39%(76). Neither measured the future HCV transmissions resulting from IDU and neither accounted for current or ex-injectors infected due to IDU conferring additional transmission risk through iatrogenic or other routes. This transmission can be through routes such as tattooing in and outside prisons(153, 367), mother-to-child transmission(306), needlestick injuries to healthcare workers(265), and general access to healthcare leading to iatrogenic transmission(122).

Policy-makers should plan the most efficient use of resources to prevent and treat HCV infections in response to the WHO's 2030 elimination targets(403). To do this, it is important to understand the future role of IDU to HCV transmission as well as the current burden of the epidemic that is among PWID. To address this knowledge gap, in this chapter I use country-specific HCV transmission modelling to estimate the contribution of IDU to HCV transmission at the country-level, regionally, and globally. I estimate the percentage of HCV infections that would be prevented from 2018-2030 if HCV transmission due to injecting risks were removed. I also investigate the factors associated with the percentage of HCV transmission due to IDU at the country-level.

7.2. Methods

The model structure, parameterisation, and calibration used in this chapter are the same as that described in Chapter 6.

7.2.1. Population attributable fraction of HCV transmission

The calibrated models for each country were used to project the HCV epidemic for 12 years from 2018 up to 2030, defined as the baseline projections for each country. To investigate the degree to which HCV transmission is driven by risks associated with IDU, the population

attributable fraction (PAF) of HCV transmission (henceforth referred to as the tPAF) due to IDU in each country, regionally, and globally, was estimated. To do this, the baseline model fits for each country were re-run with the transmission risk due to IDU set to zero from 2018 onwards. For each paired parameter set, the tPAF was estimated over 1 and 12 years as the relative reduction in the overall number of HCV infections over that period from setting the transmission risk due to IDU to zero (from 2018), compared to the baseline projections. The projections for all paired parameter sets from each country were averaged to produce country-specific estimates, which were then combined to produce regional and global estimates with the average tPAFs for each country weighted by that country's relative burden of HCV compared to the regional or global burden. The variation across the different model fits for each country were used to produce 95% credibility intervals (CrI) using the 2.5th and 97.5th percentiles of the 1,000 simulated runs, with the main estimate calculated as the median.

7.2.2. Sensitivity analyses

Sensitivity analyses investigated the effect on the tPAF estimates of: (a) general population HCV prevalence being stable, rather than declining from 1990; (b) HCV prevalence among PWID decreasing at the same rate as the general population HCV prevalence, rather than being stable; (c) the proportion of adults that are PWID in 1990 being stable in Eastern Europe and Sub-Saharan Africa, rather than increasing; (d) the same annual HCV treatment numbers, but with the treatment rate among PWID being halved and the treatment rate among people with cirrhosis being doubled; (e) the rate of initiating injecting in USA increasing 2.9-fold from 2010 onwards, to capture the recent opioid epidemic(109); and (f) varying the temporal changes in general population HCV prevalence by region.

I investigated the effect on the global tPAF estimate of only including the 66 countries with ≥2 of the key prevalence parameters having a quality rating that was scored as moderate or better (re-weighting by the new selection of countries), see table 6.7. An additional sensitivity analysis was performed by comparing the baseline scenario with a scenario where the additional transmission rate among PWID was set to zero and all infected PWID in 2018 were treated in order to completely remove transmission among PWID.

Because it is likely that there is considerable sub-national variation in HCV epidemics, there is a question about whether the tPAF estimates of our 'average' national models will reliably capture the average tPAF of a set of sub-national epidemics. I investigated this by considering a similar question, whether my tPAF estimate for an 'average' regional model approximates the combined average tPAF for the set of national models for that region. For each country in Central Asia (chosen as the first listed region), I took the weighted national prevalence estimates of HCV prevalence among PWID and the general population, and the percentage of adults that are PWID, as well as other weighted national parameters. I used the average 'regional' parameter values to calibrate a regional model for Central Asia. I compared the 12-year tPAF estimate for this regional model with the combined average regional tPAF calculated by averaging across the different national estimates (from the national models, presented in table 7.1).

All sensitivity analyses (and the main analysis for better comparison) were ran to produce 100 model fits rather than 1,000, as comparison runs show running for 100 or 1,000 fits produced very similar results (which can be seen by comparing table 7.1 with appendix table 7.4).

7.2.3. Variables associated with country-level tPAFs

I used generalised linear regression models to determine what country-level factors are associated with the tPAF of HCV due to risks associated with IDU. The 12-year tPAF was logit transformed (log(tPAF/1-tPAF)) as it is a proportion, and was regressed on the covariates for the percentage of the adult population that are PWID, HCV prevalence among PWID, HCV prevalence among the general population, the injecting duration of PWID in the country, the percentage of the country's prevalent infections that are among PWID, and the World Bank Gross National Income (GNI) per capita (which could possibly act as a confounder for the amount of spending on a country's healthcare system) – all from 2017. The non-linear association between the tPAF of HCV due to IDU and the percentage of the country's prevalent infections that are among PWID was plotted using a fractional polynomial model to accurately fit the curve.

Lastly, I undertook a regression analysis to consider how differences in the growth of each HCV epidemic affects the tPAF. This involved a mixed-effects regression analysis with country as the panel variable to account for the variation between the runs for each country. The 12-year tPAF was the dependent variable and the general population annual HCV epidemic growth as the independent variable (calculated between 2018 and 2038). For each country all of the 1,000 fitted runs were included, with the HCV prevalence growth and tPAF varying between runs.

7.3. Results

7.3.1. Fitting

The model was successfully calibrated for 88 countries. Appendix table 7.1 shows the country-level HCV transmission parameters among the general population (ranging from 0 in various countries to 0.0569 in Senegal) and PWID (ranging from 0.1533 in Nigeria to 0.9148 in Libya). Appendix table 7.2 gives the median percentage differences between the target prevalences and fitted values for the key prevalence parameters [adult % PWID: 0.0000% (95% CrI: 0.0000%, 0.0000%); PWID % chronic HCV: 0.0000% (95% CrI: 0.0000%, 23.1888%); gen-pop % chronic HCV: 0.0000% (95% CrI: 0.0000%, 19.5878%)]. Appendix table 7.3 compares the prior and posterior distributions, which, as per the results in appendix table 7.2, are similar.

Appendix figure 7.1 graphs the model fits. Note, country-level treatment numbers are already high as of 2015 in some countries, eg. 600,000 in Egypt, 15,400 in Georgia, 43,000 for Italy, and 29,700 for Spain for 2017(55). In such countries, these modelled treatment numbers result in the HCV epidemic decreasing rapidly over the next 10 to 15 years with the WHO elimination targets for incidence being reached over the modelled time period.

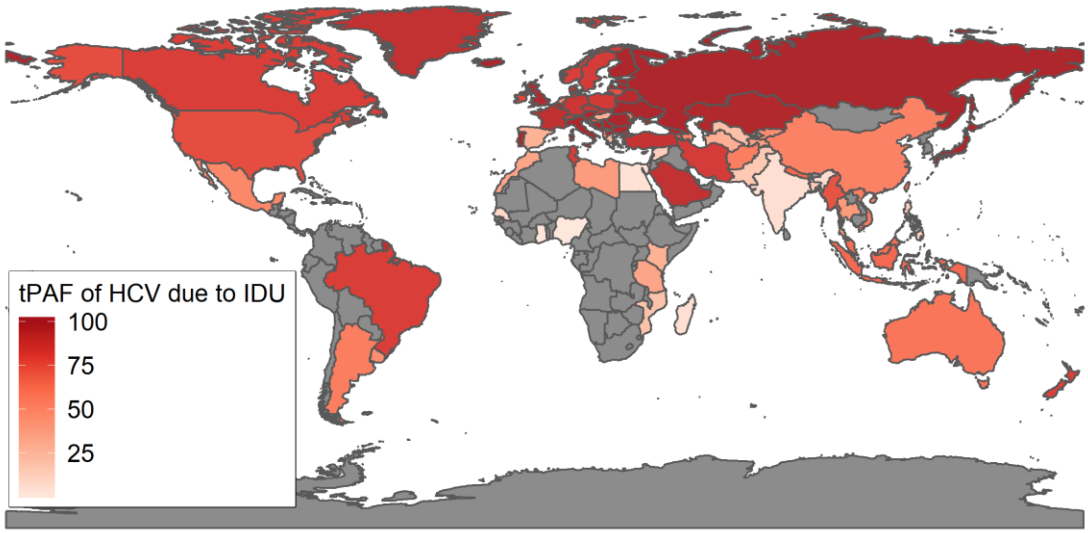
7.3.2. tPAF results

For the countries simulated, the model predicts that in 2017 0.23% (95% CrI: 0.16%, 0.31%) of the global population are PWID and 8% (95% CrI: 5%, 12%) of all prevalent HCV infections

are among people who currently inject drugs. Figures 7.1 and 7.2, and table 7.1 show the country, regional, and global estimates of the tPAF of IDU to HCV transmission for 2018 to 2030. Figure 7.3 plots the country-level 12-year tPAFs against each country's percentage of the global prevalent HCV infections.

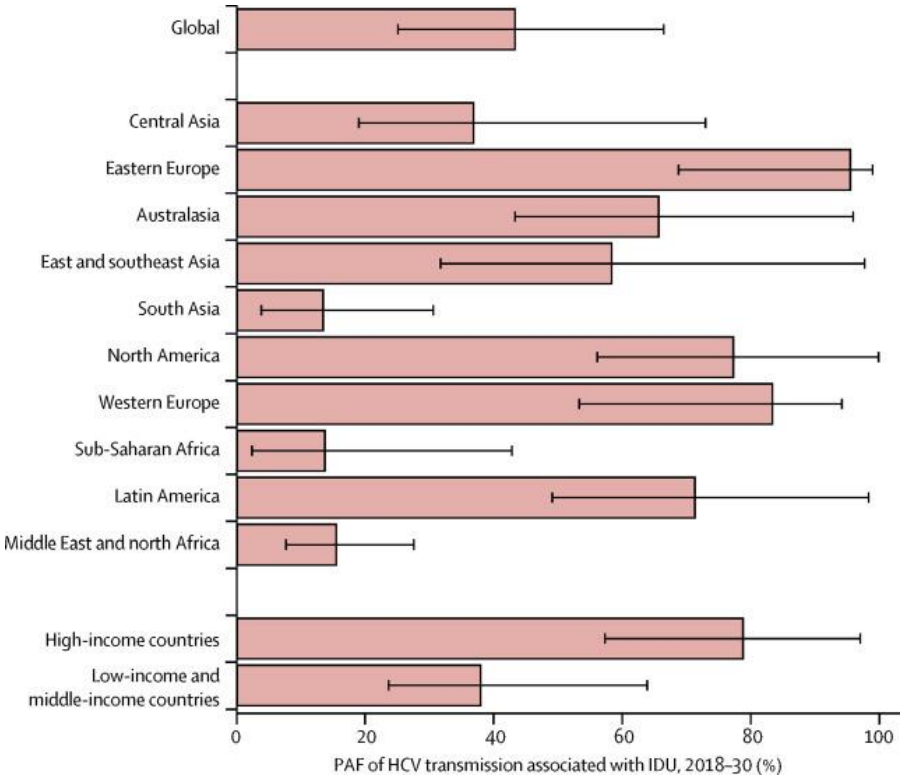
Globally, the model estimates 43% (95% CrI: 25%, 67%) of all new HCV infections could be prevented over 12-years if the heightened HCV risk associated with IDU was removed, varying from 14% (95% CrI: 2%, 43%) in Sub-Saharan Africa to 96% (95% CrI: 69%, 99%) in Eastern Europe. The 12-year tPAFs of IDU to HCV are over 50% for five other global regions: Western Europe, North America, Latin America, Australasia, and East and Southeast Asia, while they are less than 50% for Central Asia, South Asia, and Middle East and North Africa. The contribution of IDU to HCV transmission is greatest in HICs, where 79% (95% CrI: 57%, 97%) of new HCV infections could be prevented if the transmission risk due to IDU was removed, compared to 38% (95% CrI: 24%, 64%) in LMICs. The 1-year global tPAF of IDU to HCV over 2018-19, 39% (95% CrI: 21%, 64%), is slightly lower than the 12-year tPAF (2018-2030). The model also estimates that, globally, 43% (95% CrI: 24%, 80%) of infections occurring between 2018 and 2030 would be among PWID.

Figure 7.1: Map of PAF of HCV transmission due to IDU from 2018-2030*.



* Countries in grey were not modelled due to a lack of data.

Figure 7.2: Regional and global estimates for the PAF of IDU to HCV transmission from 2018-2030*.



* Medians shown in bars, with 95% credibility intervals shown with red lines.

Table 7.1: Country-level fitted demographic data values in 2017, model projections of the PAF of IDU to HCV transmission from 2018-2019 and 2018-2030, and the percentage of the setting's prevalent infections in 2017 that are among PWID*.

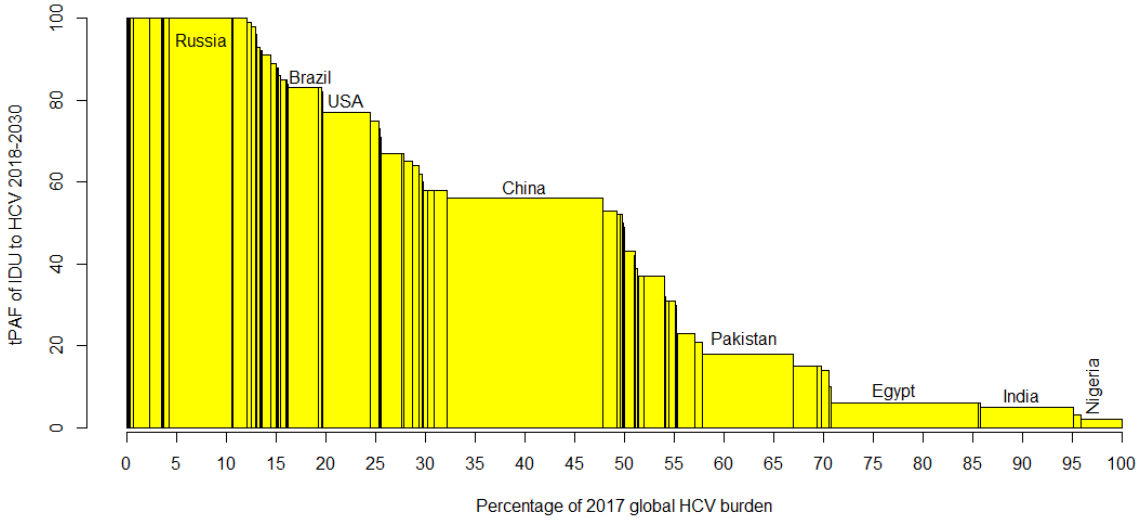
	Estimate (95% credibility interval)					
	Fitted demographic data values				tPAF of HCV infections due to IDU	
Country	**% of Adults that are PWID**	**Chronic HCV prevalence (%) among PWID**	**Chronic HCV prevalence (%) among general population**	**Percentage of the setting's prevalent infections that are among PWID**	**2018-2019**	**2018-2030**
Global	**0.32 (0.23, 0.42)**	**34.5 (25.8, 42.0)**	**1.0 (0.7, 1.4)**	**8 (5, 12)**	**39% (21%, 64%)**	**43% (25%, 67%)**
Central Asia	**0.61 (0.44, 0.81)**	**26.4 (21.0, 29.8)**	**2.4 (1.5, 3.3)**	**4 (3, 6)**	**32% (16%, 69%)**	**37% (19%, 73%)**
Kazakhstan	0.94 (0.67, 1.25)	27.4 (18.9, 30.8)	1.3 (0.8, 1.7)	14 (9, 20)	98% (60%, 100%)	99% (67%, 100%)
Kyrgyzstan	0.76 (0.56, 1.01)	21.6 (19.5, 23.6)	1.5 (0.8, 2.6)	7 (5, 10)	42% (19%, 94%)	50% (24%, 95%)
Tajikistan	0.46 (0.34, 0.62)	30.4 (27.8, 32.9)	1.5 (0.7, 2.6)	6 (4, 8)	31% (14%, 76%)	39% (19%, 81%)
Turkmenistan	0.38 (0.28, 0.48)	29.9 (24.1, 35.9)	2.0 (0.9, 2.7)	4 (3, 5)	26% (11%, 66%)	32% (15%, 72%)
Uzbekistan	0.47 (0.35, 0.63)	25.1 (21.4, 29.0)	3.6 (2.3, 4.8)	2 (2, 3)	18% (7%, 59%)	23% (9%, 64%)
Eastern Europe	**1.13 (0.71, 1.61)**	**45.8 (34.0, 53.6)**	**2.0 (1.2, 2.6)**	**21 (12, 31)**	**95% (64%, 99%)**	**96% (69%, 99%)**
Armenia	0.74 (0.47, 1.22)	36.0 (26.6, 44.5)	2.4 (1.8, 3.1)	9 (5, 15)	68% (35%, 100%)	73% (41%, 100%)
Azerbaijan	0.60 (0.51, 0.69)	48.1 (39.5, 56.1)	2.4 (1.8, 3.0)	9 (7, 11)	46% (26%, 81%)	52% (32%, 84%)
Belarus	0.57 (0.29, 0.86)	52.8 (40.3, 61.1)	1.1 (0.8, 1.7)	21 (11, 34)	96% (58%, 100%)	96% (62%, 100%)
Bosnia	0.17 (0.12, 0.21)	41.7 (34.0, 49.1)	0.1 (0.1, 0.1)	52 (36, 72)	100% (96%, 100%)	100% (97%, 100%)
Bulgaria	0.37 (0.30, 0.44)	50.0 (38.0, 54.6)	1.0 (0.6, 1.5)	15 (10, 20)	100% (62%, 100%)	100% (67%, 100%)
Czech Republic	0.64 (0.61, 0.67)	14.8 (12.0, 17.5)	0.3 (0.2, 0.4)	23 (18, 28)	80% (56%, 100%)	88% (68%, 100%)
Estonia	1.04 (0.74, 1.53)	46.6 (36.2, 57.0)	1.3 (1.1, 1.4)	32 (21, 48)	100% (89%, 100%)	100% (94%, 100%)
Georgia	4.30 (1.34, 7.32)	40.5 (28.7, 48.3)	4.6 (4.0, 5.3)	29 (10, 51)	100% (59%, 100%)	100% (70%, 100%)
Hungary	0.06 (0.04, 0.08)	34.3 (24.6, 42.2)	0.8 (0.3, 1.5)	2 (1, 3)	24% (8%, 73%)	30% (11%, 79%)
Latvia	0.90 (0.74, 1.08)	52.4 (39.6, 59.8)	1.6 (1.2, 2.0)	25 (17, 33)	100% (81%, 100%)	100% (86%, 100%)
Lithuania	0.22 (0.14, 0.31)	34.2 (27.4, 36.8)	1.1 (0.8, 1.5)	6 (4, 9)	68% (32%, 100%)	76% (42%, 100%)
Moldova	0.41 (0.29, 0.52)	41.5 (30.8, 50.4)	2.3 (1.6, 2.8)	6 (4, 8)	46% (23%, 100%)	52% (28%, 100%)
Poland	0.28 (0.21, 0.35)	49.1 (44.8, 53.0)	0.5 (0.4, 0.7)	20 (15, 27)	81% (54%, 100%)	86% (63%, 100%)
Romania	0.61 (0.48, 0.76)	62.3 (46.5, 66.5)	2.0 (1.8, 2.2)	16 (11, 21)	100% (65%, 100%)	100% (71%, 100%)
Russia	1.69 (1.06, 2.41)	47.6 (35.1, 56.6)	2.7 (1.6, 3.6)	24 (14, 36)	100% (72%, 100%)	100% (76%, 100%)
Slovakia	0.58 (0.40, 0.85)	44.1 (32.9, 55.2)	1.0 (0.7, 1.2)	21 (13, 35)	86% (55%, 100%)	88% (62%, 100%)
Ukraine	1.02 (0.62, 1.54)	37.0 (25.4, 41.3)	2.0 (1.0, 2.7)	15 (9, 23)	100% (54%, 100%)	100% (59%, 100%)

Country	Fitted demographic data values			Percentage of the setting's prevalent infections that are among PWID	tPAF of HCV infections due to IDU	
	% of Adults that are PWID	Chronic HCV prevalence (%) among PWID	Chronic HCV prevalence (%) among general population		2018-2019	2018-2030
Australasia	**0.60 (0.46, 0.73)**	**35.7 (32.0, 39.3)**	**0.8 (0.7, 1.1)**	**19 (13, 24)**	**58% (34%, 94%)**	**66% (43%, 96%)**
Australia	0.58 (0.45, 0.70)	32.4 (29.7, 35.1)	0.8 (0.7, 1.0)	17 (12, 21)	54% (32%, 93%)	62% (41%, 95%)
New Zealand	0.69 (0.51, 0.87)	50.6 (42.8, 57.1)	1.0 (0.6, 1.4)	26 (19, 34)	74% (45%, 100%)	82% (57%, 100%)
East & Southeast Asia	**0.23 (0.19, 0.28)**	**31.5 (23.8, 38.2)**	**0.7 (0.5, 1.0)**	**7 (5, 10)**	**53% (26%, 98%)**	**58% (32%, 98%)**
China	0.22 (0.18, 0.27)	27.1 (19.5, 35.0)	0.7 (0.6, 0.9)	6 (4, 9)	50% (24%, 100%)	56% (30%, 100%)
Indonesia	0.11 (0.09, 0.12)	57.5 (54.3, 60.4)	0.5 (0.2, 0.8)	9 (7, 11)	61% (27%, 100%)	67% (32%, 100%)
Japan	0.44 (0.36, 0.53)	32.9 (23.5, 40.6)	0.6 (0.4, 1.0)	19 (13, 26)	100% (68%, 100%)	100% (76%, 100%)
Malaysia	1.26 (1.09, 1.43)	42.6 (32.5, 45.7)	1.8 (0.6, 3.8)	20 (15, 24)	57% (26%, 100%)	65% (32%, 100%)
Myanmar	0.47 (0.35, 0.59)	19.4 (13.5, 21.5)	1.0 (0.6, 1.4)	6 (5, 9)	70% (35%, 100%)	75% (42%, 100%)
Philippines	0.04 (0.03, 0.05)	24.9 (14.9, 35.4)	0.5 (0.2, 0.8)	1 (1, 2)	11% (3%, 35%)	14% (5%, 42%)
Taiwan	0.27 (0.20, 0.34)	55.6 (48.5, 59.9)	1.8 (1.0, 3.1)	7 (5, 9)	57% (18%, 100%)	64% (22%, 100%)
Thailand	0.10 (0.05, 0.16)	55.7 (51.9, 59.4)	1.0 (0.5, 1.9)	5 (2, 7)	38% (11%, 100%)	43% (13%, 100%)
Viet Nam	0.23 (0.18, 0.27)	37.5 (29.7, 45.7)	0.9 (0.7, 1.1)	7 (5, 9)	52% (28%, 100%)	58% (34%, 100%)
South Asia	**0.09 (0.07, 0.11)**	**30.3 (16.2, 44.0)**	**0.9 (0.6, 1.3)**	**2 (1, 3)**	**10% (3%, 25%)**	**14% (4%, 31%)**
Afghanistan	0.80 (0.56, 1.03)	30.5 (23.6, 36.9)	0.9 (0.5, 1.3)	15 (10, 22)	46% (23%, 98%)	58% (32%, 99%)
Bangladesh	0.07 (0.06, 0.07)	27.7 (20.3, 34.9)	0.9 (0.3, 1.4)	1 (1, 2)	12% (5%, 37%)	15% (6%, 43%)
India	0.02 (0.01, 0.03)	31.2 (27.4, 35.0)	0.7 (0.4, 1.0)	1 (0, 1)	4% (2%, 11%)	6% (2%, 15%)
Iran	0.27 (0.21, 0.34)	35.5 (25.4, 44.8)	0.4 (0.2, 0.6)	18 (12, 26)	78% (45%, 100%)	85% (55%, 100%)
Nepal	0.20 (0.19, 0.21)	35.7 (27.7, 44.0)	0.5 (0.4, 0.6)	10 (8, 13)	60% (34%, 100%)	67% (42%, 100%)
Pakistan	0.36 (0.32, 0.40)	28.3 (7.3, 52.9)	3.0 (2.7, 3.4)	2 (1, 4)	13% (2%, 37%)	18% (2%, 47%)
North America	**1.08 (0.63, 1.51)**	**30.7 (22.2, 40.7)**	**0.9 (0.6, 1.2)**	**30 (16, 47)**	**67% (43%, 100%)**	**77% (56%, 100%)**
Canada	0.37 (0.30, 0.43)	50.7 (42.4, 63.2)	0.6 (0.4, 0.8)	23 (17, 30)	74% (44%, 100%)	83% (56%, 100%)
USA	1.16 (0.67, 1.63)	30.0 (21.2, 40.0)	0.9 (0.6, 1.2)	30 (16, 48)	67% (43%, 100%)	77% (56%, 100%)
Western Europe	**0.32 (0.23, 0.40)**	**37.9 (27.3, 44.7)**	**0.6 (0.3, 1.0)**	**15 (10, 20)**	**80% (45%, 93%)**	**83% (53%, 94%)**
Albania	0.39 (0.28, 0.48)	25.5 (17.3, 30.1)	1.7 (1.3, 2.2)	5 (3, 6)	55% (22%, 100%)	60% (26%, 100%)
Austria	0.30 (0.22, 0.37)	34.0 (27.3, 38.9)	0.3 (0.1, 0.4)	31 (21, 42)	100% (69%, 100%)	100% (79%, 100%)
Belgium	0.35 (0.26, 0.45)	38.1 (28.5, 47.3)	0.4 (0.2, 0.6)	25 (16, 36)	100% (53%, 100%)	100% (61%, 100%)
Croatia	0.23 (0.19, 0.27)	26.3 (21.5, 31.2)	0.6 (0.4, 0.8)	9 (7, 12)	66% (29%, 100%)	71% (34%, 100%)
Cyprus	0.08 (0.05, 0.11)	35.1 (31.0, 39.5)	0.4 (0.3, 0.8)	4 (3, 6)	28% (10%, 78%)	35% (13%, 84%)

Country	Fitted demographic data values			Percentage of the setting's prevalent infections that are among PWID	tPAF of HCV infections due to IDU	
	% of Adults that are PWID	Chronic HCV prevalence (%) among PWID	Chronic HCV prevalence (%) among general population		2018-2019	2018-2030
Denmark	0.42 (0.35, 0.48)	27.3 (23.4, 31.2)	0.4 (0.3, 0.4)	26 (20, 31)	89% (51%, 100%)	92% (60%, 100%)
FYROM (Macedonia)	0.15 (0.11, 0.19)	45.1 (42.4, 47.6)	0.3 (0.2, 0.4)	17 (13, 22)	97% (54%, 100%)	98% (61%, 100%)
Finland	0.48 (0.41, 0.61)	47.7 (36.6, 52.8)	0.5 (0.4, 0.7)	33 (24, 43)	100% (84%, 100%)	100% (87%, 100%)
France	0.19 (0.16, 0.22)	35.9 (28.5, 45.0)	0.3 (0.2, 0.5)	16 (12, 21)	90% (50%, 100%)	93% (62%, 100%)
Germany	0.22 (0.07, 0.37)	40.9 (36.4, 44.8)	0.4 (0.2, 0.5)	21 (7, 36)	83% (34%, 100%)	89% (44%, 100%)
Greece	0.07 (0.06, 0.08)	45.4 (42.2, 48.5)	1.0 (0.4, 1.5)	3 (2, 3)	19% (8%, 64%)	23% (10%, 70%)
Iceland	0.23 (0.17, 0.29)	24.4 (18.9, 28.3)	0.2 (0.1, 0.3)	25 (16, 36)	100% (78%, 100%)	100% (82%, 100%)
Ireland	0.26 (0.21, 0.32)	49.5 (46.0, 52.2)	0.6 (0.4, 0.9)	17 (13, 21)	70% (37%, 100%)	79% (46%, 100%)
Italy	0.80 (0.59, 1.02)	35.5 (19.8, 42.4)	1.7 (0.9, 3.2)	13 (7, 19)	100% (47%, 100%)	100% (55%, 100%)
Luxembourg	0.56 (0.46, 0.65)	47.5 (39.2, 52.7)	0.6 (0.4, 0.9)	29 (23, 36)	88% (56%, 100%)	94% (72%, 100%)
Malta	0.27 (0.21, 0.33)	18.8 (14.3, 23.8)	0.2 (0.2, 0.3)	15 (13, 21)	72% (36%, 100%)	79% (45%, 100%)
Montenegro	0.37 (0.27, 0.47)	30.1 (21.4, 34.4)	0.8 (0.6, 1.0)	11 (7, 15)	100% (64%, 100%)	100% (69%, 100%)
Netherlands	0.03 (0.02, 0.04)	30.3 (19.3, 35.7)	0.1 (0.0, 0.2)	7 (4, 9)	41% (18%, 88%)	52% (25%, 91%)
Norway	0.24 (0.21, 0.27)	40.2 (37.0, 43.5)	0.3 (0.3, 0.4)	22 (18, 26)	74% (47%, 100%)	83% (61%, 100%)
Portugal	0.21 (0.18, 0.23)	53.9 (42.1, 61.8)	0.7 (0.3, 1.1)	14 (10, 17)	100% (54%, 100%)	100% (67%, 100%)
Serbia	0.49 (0.42, 0.55)	17.1 (12.4, 20.8)	0.4 (0.3, 0.4)	19 (14, 25)	100% (85%, 100%)	100% (88%, 100%)
Slovenia	0.40 (0.31, 0.50)	20.2 (15.8, 23.0)	0.3 (0.2, 0.3)	24 (18, 32)	93% (54%, 100%)	95% (64%, 100%)
Spain	0.07 (0.05, 0.09)	43.1 (32.4, 46.9)	0.8 (0.3, 1.4)	3 (2, 4)	22% (8%, 60%)	31% (13%, 69%)
Sweden	0.22 (0.06, 0.49)	52.1 (48.2, 67.1)	0.3 (0.3, 0.4)	26 (7, 60)	73% (29%, 100%)	85% (45%, 100%)
Switzerland	0.23 (0.20, 0.27)	46.4 (40.8, 51.9)	0.6 (0.4, 0.8)	14 (11, 17)	77% (38%, 100%)	85% (51%, 100%)
UK	0.42 (0.37, 0.45)	42.0 (33.5, 49.8)	0.4 (0.3, 0.5)	33 (24, 42)	97% (73%, 100%)	98% (83%, 100%)
Sub-Saharan Africa	**0.40 (0.26, 0.55)**	**14.2 (10.5, 17.7)**	**1.4 (0.9, 2.2)**	**3 (1, 4)**	**11% (2%, 39%)**	**14% (2%, 43%)**
Ghana	0.05 (0.04, 0.06)	29.8 (26.5, 33.0)	1.8 (1.0, 3.2)	1 (0, 1)	2% (1%, 6%)	3% (1%, 8%)
Kenya	0.12 (0.05, 0.18)	18.8 (13.2, 24.5)	0.4 (0.2, 0.6)	3 (1, 5)	22% (8%, 51%)	31% (13%, 61%)
Madagascar	0.22 (0.06, 0.51)	5.3 (2.0, 9.6)	0.6 (0.5, 0.9)	1 (0, 3)	4% (0%, 18%)	6% (1%, 27%)
Mauritius	0.82 (0.47, 1.33)	70.9 (54.3, 74.0)	1.5 (1.1, 1.9)	29 (17, 48)	88% (55%, 100%)	90% (59%, 100%)
Mozambique	0.20 (0.05, 0.36)	49.4 (46.1, 52.6)	1.6 (0.4, 3.9)	3 (1, 6)	17% (3%, 59%)	21% (4%, 67%)
Nigeria	0.36 (0.26, 0.46)	4.0 (2.6, 5.8)	1.4 (1.3, 1.6)	1 (0, 1)	1% (0%, 3%)	2% (0%, 4%)
Senegal	0.08 (0.06, 0.10)	33.4 (27.5, 39.0)	1.0 (0.2, 2.5)	1 (1, 2)	7% (2%, 31%)	10% (3%, 41%)

Country	Fitted demographic data values			Percentage of the setting's prevalent infections that are among PWID	tPAF of HCV infections due to IDU	
	% of Adults that are PWID	Chronic HCV prevalence (%) among PWID	Chronic HCV prevalence (%) among general population		2018-2019	2018-2030
Tanzania	1.23 (0.84, 1.63)	20.0 (16.5, 23.9)	2.4 (0.7, 4.5)	6 (4, 8)	29% (9%, 87%)	37% (13%, 91%)
Latin America	**0.44 (0.35, 0.53)**	**49.7 (44.1, 52.8)**	**0.8 (0.7, 1.0)**	**18 (14, 23)**	**66% (41%, 98%)**	**71% (49%, 98%)**
Argentina	0.29 (0.28, 0.32)	41.1 (38.3, 43.9)	0.8 (0.4, 1.2)	11 (9, 12)	51% (25%, 99%)	58% (31%, 99%)
Brazil	0.63 (0.50, 0.76)	47.1 (41.0, 50.2)	0.9 (0.8, 1.1)	23 (18, 30)	77% (49%, 100%)	83% (59%, 100%)
Mexico	0.17 (0.13, 0.22)	72.4 (69.1, 75.2)	0.7 (0.6, 0.9)	12 (8, 15)	48% (27%, 94%)	53% (32%, 95%)
Uruguay	0.39 (0.15, 0.75)	16.3 (14.4, 18.4)	0.6 (0.5, 0.8)	8 (3, 15)	43% (16%, 100%)	49% (20%, 100%)
Middle East & North Africa	**0.24 (0.17, 0.30)**	**31.7 (23.6, 36.8)**	**2.5 (2.0, 3.1)**	**2 (1, 3)**	**13% (6%, 25%)**	**16% (8%, 28%)**
Egypt	0.21 (0.14, 0.26)	26.1 (18.8, 33.7)	6.3 (5.3, 7.6)	1 (0, 1)	3% (1%, 9%)	5% (2%, 12%)
Israel	0.41 (0.30, 0.51)	28.3 (24.3, 32.6)	0.9 (0.6, 1.1)	9 (6, 12)	28% (14%, 59%)	37% (20%, 69%)
Lebanon	0.14 (0.10, 0.18)	15.6 (11.3, 20.6)	0.2 (0.1, 0.4)	7 (4, 10)	35% (14%, 86%)	46% (20%, 92%)
Libya	0.05 (0.02, 0.08)	65.0 (62.0, 68.2)	0.6 (0.5, 0.7)	3 (1, 6)	35% (12%, 86%)	42% (15%, 89%)
Morocco	0.13 (0.08, 0.18)	38.0 (26.9, 48.3)	0.8 (0.6, 1.0)	5 (2, 7)	29% (11%, 72%)	37% (16%, 80%)
Saudi Arabia	0.19 (0.13, 0.24)	50.8 (45.1, 54.3)	0.3 (0.3, 0.4)	19 (14, 25)	88% (54%, 100%)	92% (65%, 100%)
Syria	0.06 (0.04, 0.08)	43.6 (32.6, 53.5)	1.3 (0.5, 1.9)	1 (1, 2)	12% (4%, 34%)	15% (6%, 41%)
Tunisia	0.20 (0.14, 0.25)	28.2 (23.4, 32.5)	0.5 (0.2, 0.8)	8 (6, 11)	79% (35%, 100%)	84% (43%, 100%)
Turkey	0.40 (0.30, 0.50)	30.9 (21.8, 33.6)	0.7 (0.5, 1.1)	11 (8, 16)	89% (47%, 100%)	91% (54%, 100%)

Figure 7.3: Bar chart of each country's PAF of IDU to HCV transmission 2018-2030 against the percentage of the global prevalent HCV infections (2017) in that country*.



* Countries with the largest chronic HCV burdens in 2017 are labelled.

7.3.3. Sensitivity analyses

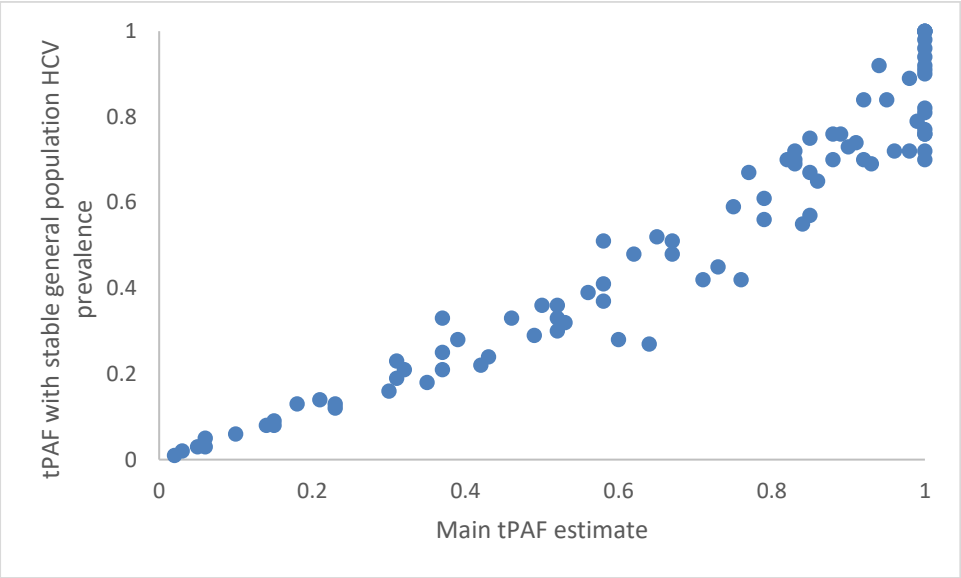
Figure 7.4, table 7.2, and appendix table 7.4 show the results of various sensitivity analyses, with the most important changes indicating the tPAF could be lower, 33% (95% CrI: 20%, 54%), if the HCV prevalence trends among the general population were assumed to be stable instead of decreasing, or 30% (95% CrI: 15%, 51%) if trends varied by region. There were large changes for the tPAF of individual countries for these two sensitivity analyses. For example, Australia's tPAF drops from 66% (95% CrI: 41%, 10%) in the main analysis to 48% (95% CrI: 32%, 81%) when assuming a stable general population HCV prevalence, or 44% (95% CrI: 27%, 75%) when assuming that epidemic trajectories vary by region. Sensitivity analyses also showed that the tPAF for USA rose from 67% (95% CrI: 41%, 100%) in the baseline model to 85% (95% CrI: 62%, 100%) when I assumed an increasing epidemic of IDU since 2010 (table 7.3). This increase occurs due to there being 2.9 times more PWID in the modified model during the analysis period than for the baseline model. The sensitivity analyses where I separately assumed (i) a decreasing HCV prevalence among PWID, (ii) the population percentage of PWID in Eastern Europe and Sub-Saharan Africa was stable from 1990 (rather than increasing), (iii) treatment rates are halved among PWID and doubled among people with cirrhosis, did not alter the global tPAF estimate (all 43%). For the

analysis including only the 66 countries with better data, the global average tPAF increases slightly to 49% (95% CrI: 29%, 73%). Table 7.4 shows that the global tPAF increases to 46% (95% CrI: 26%, 65%) if the heightened burden of HCV among PWID was also removed as well as their elevated transmission risk.

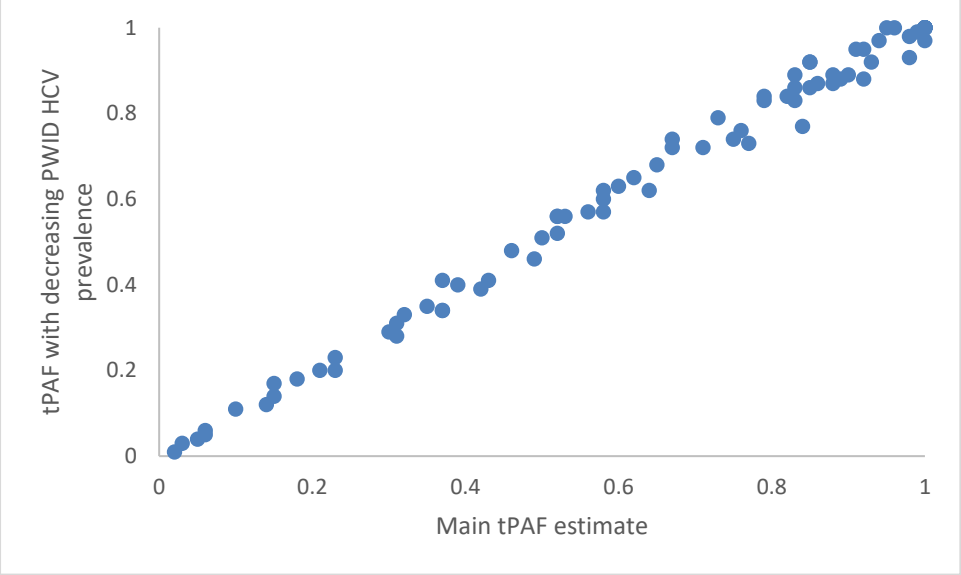
The regional 'average' model for Central Asia produced very similar results, with a tPAF of 34% (95% CrI: 19%, 71%), compared to the average tPAF across the different national models of 37% (95% CrI: 19%, 73%).

Figure 7.4: Scatter plots of country-level results of the main 2018-2030 tPAF estimates against sensitivity analysis results.

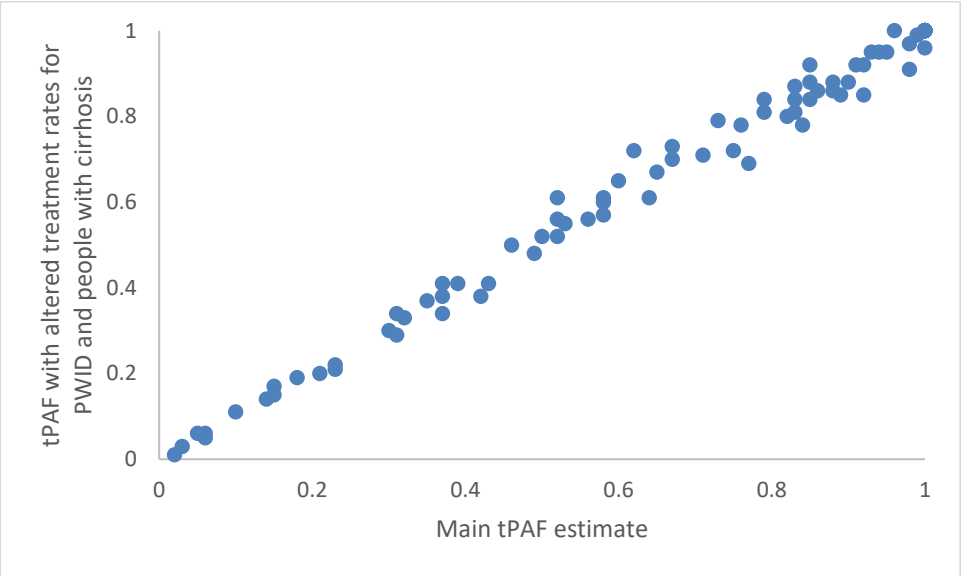
7.4a) Assuming stable general population HCV prevalence.



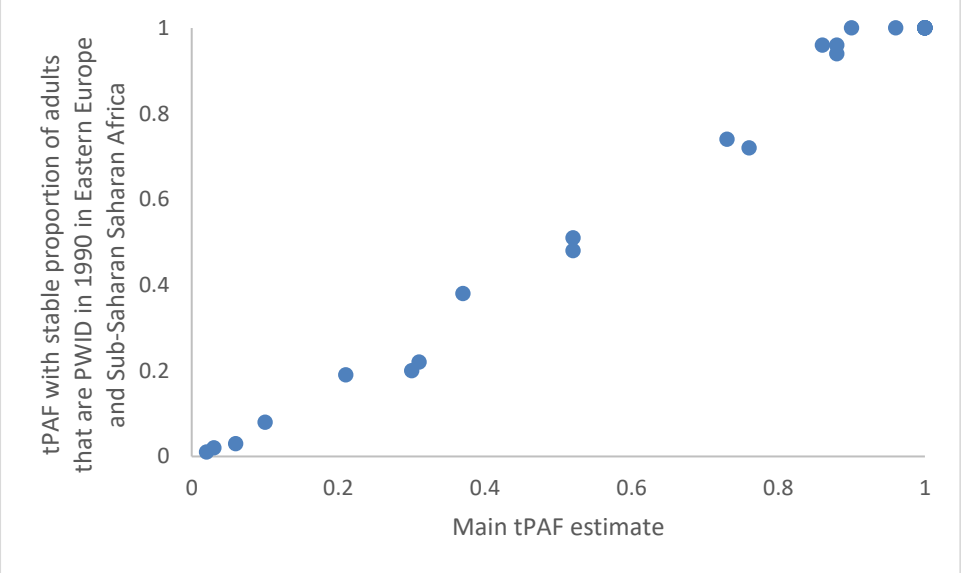
7.4b) Assuming decreasing PWID HCV prevalence.



7.4c) Assuming altered treatment rates are halved among PWID and doubled among people with cirrhosis.



7.4d) Assuming the proportion of adults that are PWID was stable in 1990 in Eastern Europe and Sub-Saharan Africa.



7.4e) Assuming varied HCV epidemic trajectories by region.

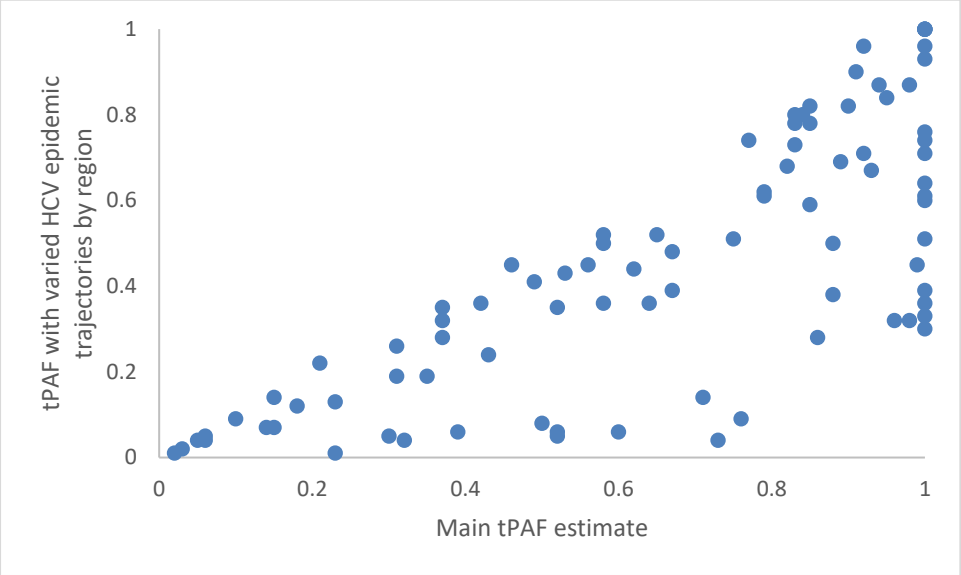


Table 7.2: Sensitivity analysis where the proportion of adults that are PWID in the USA expands from 2010 onwards*.

Assumptions	Fitted demographic data values			Percentage of the setting's prevalent infections that are among PWID	tPAF of HCV infections due to IDU
	% of Adults that are PWID	Chronic HCV prevalence (%) among PWID	Chronic HCV prevalence (%) among general population		2018-2030
Original	1.19 (0.72, 1.69)	30.2 (20.9, 41.2)	0.9 (0.5, 1.2)	29 (13, 50)	67% (41%, 100%)
Expanding PWID epidemic	2.18 (1.47, 3.19)	18.1 (12.3, 26.3)	0.9 (065, 1.3)	34 (16, 55)	85% (62%, 100%)

*From 2010 onwards the rate of initiating injecting is multiplied by 2.9 due to evidence of incidence of viral hepatitis C increasing by this amount between 2010 and 2015(57), which is thought to be driven by an increase in injecting drug use(330).

Table 7.3: tPAF of IDU to HCV for 2018-2030 and percentages of incident infections 2018-2030 among the general population that would be avoided if all HCV among PWID was treated in 2018 and transmission was reduced to levels in the general population*.

	Infections avoided among general population	**2018-2030 tPAF**	
Country	**Percentage (95% Credibility Intervals)**	**Main analysis**	**Treating all PWID in 2018**
Global	**6% (3%, 12%)**	43% (24%, 66%)	46% (26%, 65%)
Central Asia	6% (3%, 12%)	36% (18%, 76%)	39% (21%, 72%)
Eastern Europe	15% (10%, 21%)	96% (65%, 99%)	96% (70%, 99%)
Australasia	27% (20%, 39%)	69% (43%, 100%)	75% (52%, 100%)
East & Southeast Asia	11% (6%, 19%)	58% (29%, 95%)	60% (33%, 95%)
South Asia	4% (1%, 8%)	13% (4%, 30%)	16% (5%, 29%)
North America	42% (28%, 53%)	77% (54%, 100%)	87% (64%, 100%)
Western Europe	17% (10%, 26%)	83% (54%, 95%)	83% (56%, 94%)
Sub-Saharan Africa	4% (1%, 12%)	13% (3%, 42%)	14% (4%, 44%)
Latin America	21% (14%, 28%)	75% (48%, 98%)	78% (54%, 99%)
Middle East & North Africa	2% (1%, 3%)	16% (8%, 26%)	16% (8%, 27%)

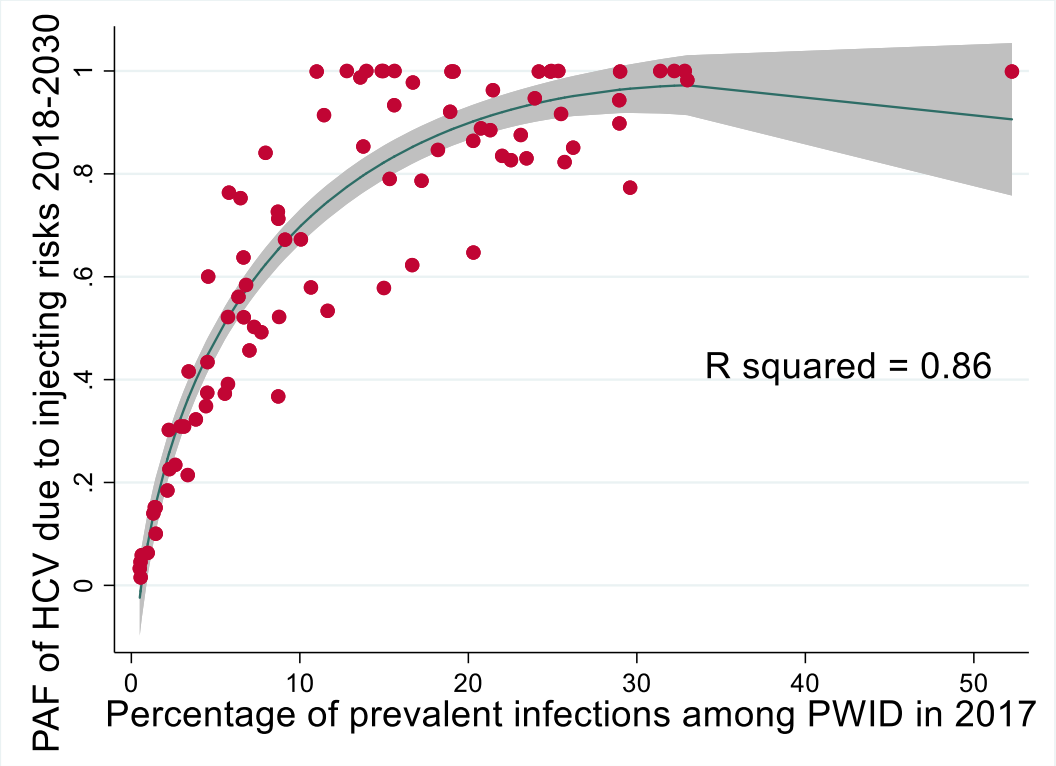
* The extra transmission among PWID was 0.

7.3.4. Associations of tPAF and country-level variables

Figure 7.5 shows there is a strong, positive association between the 12-year tPAF for each country and the percentage of the country's prevalent infections that are among PWID. In univariable regression analyses (table 7.4), the logit transformed country-level tPAF increases linearly with the percentage of a country's prevalent infections that are among PWID [OR 0.09 (95% CrI: 0.02, 0.17), R^2 0.31], the country's GNI coefficient [OR 0.05 (95% CrI: 0.00, 0.10), R^2 0.05], HCV prevalence among PWID [OR 0.09 (95% CrI: 0.02, 0.17), R^2 0.07], and the population percentage of PWID [OR 2.62 (95% CrI: 0.75, 4.49), R^2 0.08]. In the multivariable model, only the percentage of a country's prevalent infections that are among PWID was associated with higher 12-year tPAF [aOR 0.26 (95% CrI: 0.13, 0.38), R^2 0.36].

The mixed-effects regression analysis across the 1000 fitted runs for each country found that a higher annual general population HCV prevalence growth was associated with a 3.35% lower tPAF [-3.35% (95% CI: -3.52%, -3.18%)] per percentage point increase in general population HCV prevalence (from 2017 to 2038).

Figure 7.5: Scatter plot of the association between the PAF of IDU to HCV transmission from 2018-2030 and the percentage of the country's prevalent infections that are among PWID in 2017 for each country*.



* The blue line is a plotted line of best fit* and the grey area is the 95% confidence interval. Model equation: tPAF=-0.3149-(0.0372*P_PWID)+(0.4376*P_PWID$^{1/2}$), where P_PWID is the percentage of the country's prevalent infections that are among PWID.

Table 7.4: Univariable and multivariable associations between the PAF of IDU to HCV transmission from 2018-2030† and demographic and epidemic-related variables.

	Dependent variable: tPAF (logit transformed) Coefficient (95% confidence interval)	
Variable*	**Univariable**	**Multivariable**
GNI per capita (per $1000 US dollars)**	0.05 (0.00, 0.10) [p=0.039]	0.01 (-0.04, 0.07) [p=0.64]
Population percentage of PWID in adults	2.62 (0.75, 4.49) [p=0.0066]	1.14 (-1.21, 3.50) [p=0.34]
HCV prevalence among PWID***	0.09 (0.02, 0.17) [p=0.014]	0.05 (-0.02, 0.12) [p=0.12]
HCV prevalence among general population***	-0.29 (-1.34, 0.75) [p=0.58]	-0.07 (-1.28, 1.13) [p=0.903]
Injecting duration (years)	0.21 (-0.00, 0.42) [p=0.053]	-0.22 (-0.46, 0.02) [p=0.071]
Percentage of the country's prevalent infections that are among PWID	0.26 (0.18, 0.34) [p<0.0001]	0.26 (0.13, 0.38) [p<0.0001]

GNI: Gross National Income

† Logit transformed

* All variables are from 2017 except for injecting duration which is taken from surveys covering a variety of years for each country.

** Syria is missing data on GNI per capita.

*** HCV prevalence measures are used here as proportions, not percentages

7.4. Discussion

7.4.1. Main findings

Despite PWID comprising less than 0.5% of the global adult population in 2017 and only contributing 8% of prevalent infections, removing the transmission risk due to IDU could prevent nearly one-half (43%) of all new HCV infections globally from 2018-2030. This varied by country and regions. In Sub-Saharan Africa, where the epidemic is thought to be driven by medical transmission(185), just over one-tenth of infections are due to the elevated risk associated with IDU, whereas in Eastern Europe it is over nine-tenths of infections. In HICs, about twice as many infections (79%) would be prevented from removing the transmission risk due to IDU than in LMICs (38%). Interestingly, the percentage of a country's prevalent infections that are among PWID is strongly, positively associated with the tPAF, as this takes into account the size of the PWID population as well as the prevalence of HCV among them. For example, if 5% of the country's prevalent infections are among current injectors then the estimated tPAF is 48%, which increases to 70% if 10% of prevalent infections are among PWID.

7.4.2. Comparison with other literature

To my knowledge, no paper has estimated the future contribution of IDU-related risk to HCV transmission at a global level. Two papers have estimated the current contribution of IDU to the global burden of HCV infection or disease(76, 127), but neither accounted for the chain of transmission that can occur in the general population due to individuals that were infected through IDU. Degenhardt et al. estimated that 39% of disability adjusted life years (DALYs) for HCV in 2013 were due to IDU(76), consistent with the magnitude of my estimate despite using a very different outcome and methodology. Grebely et al. calculated 8.5% of all prevalent HCV infections globally were among PWID, comparable to our estimate of 8% for prevalent infections in 2017(127). Grebely et al.'s estimate is useful for guiding screening and treatment campaigns but does not address the importance of IDU to future HCV transmission. A detailed modelling analysis by Heffernan et al. estimated that globally 29% (95% CrI: 27%, 32%) of new infections between 2016 and 2030 would be among PWID(150). That is a different concept to the tPAF calculated in this chapter as it does not account for the entire contribution of PWID to the HCV epidemic. Similar to the result I

found for the tPAF of IDU to HCV (43%), I found the percentage of new infections between 2018 and 2030 that will be among PWID to be 43% (95% CrI: 24%, 80%). This estimate is similar to that of Heffernan et al. when considering the overlapping intervals, with any discrepancy likely due to Heffernan et al. extrapolating regional prevalence data to countries where it was missing, which tended to be areas with lower percentages of infections among PWID, such as Sub-Saharan Africa(150). Otherwise, global modelling by Blach et al. simulated the overall HCV epidemics in different countries but did not dynamically model HCV transmission or the role of IDU(40). Lastly, my results appear to broadly agree with national estimates of the burden of HCV due to injecting risks in the Netherlands and the UK(143, 385). These analyses suggest that 28% of current infections in the Netherlands are due to IDU(385), within the credibility intervals of my estimate (3-31%), and 34% of the UK's current HCV burden is among PWID(143), very similar to my projections [33% (95% CrI: 24%-42%)].

Lastly, it is important to note that the tPAF used in this chapter differs from the PAF used in chapter 3, which is based on the relative risks of being infected. The tPAF ("transmission PAF") used here looks at the effect of reducing the modelled additional transmission rate associated with a particular risk factor (IDU) to 0, whereas the PAF calculation used in chapter 3 reduces the risk ratio associated with a particular variable in observational data to 0. The tPAF is likely to produce more accurate quantification of the importance of a risk factor as it is in effect looking at a modelled causal relationship, whilst the PAF used in chapter 3 only looks at observed associations and cannot capture onward transmission. However, the simulation approach tends to lead to larger PAF estimates than the observed risk ratio approach due to how both methods account for population mixing(47). Also, my measure for the transmission PAF can differ to other estimations as discussed in Brooks-Pollock and Danon(47). My tPAF more relates to the proportion of transmission that could be prevented if a certain risk behaviour was removed or made safe, whereas Brooks-Pollock and Danon develop another approach that relates to the proportion of infections that result through a specific risk factor, which in some situations may be less than the proportion of infections that could be prevented from removing a risk behaviour(47).

7.4.3. Strengths and limitations

My modelling is comprehensive in coverage as the analysis uses data from HCV epidemics in 88 countries, comprising 85% of the world's population. I account for the role of heightened risk among PWID in these HCV epidemics, and incorporate country-level demographic information, population growth, and vertical transmission. Importantly, I account for all incident infections that result from individuals infected due to IDU, and the effect this has on the HCV incidence and prevalence among the general population. This enables me to more accurately estimate the role that IDU has on the overall epidemics in each country. Despite this, my analysis has limitations.

The data on the prevalence of IDU, and the prevalence of HCV amongst PWID and the general population were variable in quality, possibly impacting on my results. For the former two quantities this is partly due to the illicit nature of IDU, which makes PWID a difficult population to study and to enumerate accurately. Data for these three quantities came from existing systematic reviews, and I modelled all countries that had an estimate for each. This meant that for some data estimates it was unclear how they were compiled, some were old, and some were uncertain.

Taking data from disparate sources means some of country-level tPAF estimates may be imprecise. However, it is hard to quantify how this affects my results without additional data. Data-quality scores are shown in table 6.8, with 46% of countries having a low scored general population HCV prevalence estimate, and 20% and 39% of country estimates for HCV prevalence among PWID and the proportion of adults that inject drugs, respectively, having low scores. Although the majority of these key data points scored highly, only 19 countries had all three of these key prevalence parameters scored as moderate or better, whilst 66 countries have at least two of these parameters scored moderate or better. These 19 and 66 countries account for 32% and 76% of the global population, respectively. It is possible that the PAF projections for the remaining countries may change when better data becomes available, with better data being most needed for the HCV prevalence in the general population and the size estimates of PWID populations. When only considering the 66 countries with better data, the global average PAF increases slightly to 49% emphasising that not including projections from the countries with worse quality data does not substantially affect my projections. This higher estimate could be due to countries with

better scored estimates mostly being high-income countries where the contribution of IDU to HCV transmission is generally greater.

Additionally, some country's tPAF estimates were lower than expected, including Spain (31%), Greece (23%), and Australia (62%); previous evidence for these countries has suggested most transmission was among IDU(16). This discrepancy may be due to data issues, or HCV-epidemic factors, such as historically high levels of IDU that have now decreased, under-estimates of PWID prevalence, or possibly high numbers of migrants with higher HCV risk than the background population. Other modelling from the Netherlands has suggested that most HCV infections were among migrants(385). I did not incorporate migration in our model due to insufficient data to do this and uncertainty around key assumptions, such as their HCV prevalence(378). Although not explicitly included, I would consider incoming infections due to migration as something that contributes to the non-IDU transmission aspect of the model, just as I would for medical and community transmission. Similarly, I was unable to include HCV epidemics among MSM within the model due to a scarcity of information around prevalences globally. However, studies indicate that although transmission among MSM is much higher than among heterosexual couples, incidence and prevalence is still low compared with PWID(414) and likely contributes little to the epidemic in comparison(225). Additionally, the model cannot accurately estimate the percentage of the population that are ex-injectors or the percentage of infections that are among ex-injectors as the model started in 1990 and even modelling further back would not necessarily create accurate estimates due to a lack of information about how the prevalence of IDU has changed over time.

I also did not explicitly model what makes up the non-IDU component of HCV transmission, which could be due to medical injections, tattooing, body-piercing, barbering, etc. Unfortunately, detailed country-level data on these behaviours were unavailable. Despite these issues, other country-level estimates seem to agree with my model(143, 385), with the low tPAFs of IDU in some HICs implying that our global tPAF estimate for IDU may be conservative. Also, general insights about how the tPAF is related to different country-level factors should still hold.

Another limitation of my analysis is that my deterministic models did not capture the network effects of how HCV transmits among PWID, which has been shown to be important for assessing the impact of interventions for HCV(323, 421). This chapter is less concerned

with this question; rather its main aim is to determine how the observed epidemic among PWID may contribute to overall levels of transmission in that country. Although I acknowledge that network models can better represent transmission dynamics among PWID (if sufficient data exists to parameterise them) and the impact of interventions, when both types of model are parameterised and calibrated to the same HCV prevalence data (with the same population turnover parameters) the resulting incidence projections from a mass action model will closely match those of the network model(88, 151, 180, 251).

For almost all countries included, there is little to no published data to determine the likely ongoing evolution of each country's HCV epidemic. To counter this, I gathered available evidence on reductions in HCV transmission risks due to improved blood transfusion safety(291) or reductions in unsafe medical injections(283), and so assumed that the modelled global epidemic was in decline, consistent with modelling by Blach et al(40). However, there is considerable uncertainty in this assumption, so I assumed wide uncertainty bounds and undertook sensitivity analyses where I either assumed each country's HCV prevalence trends were stable or varied by region, which both projected lower tPAFs (about 30-33%). Importantly, country-level HCV epidemic trajectories are highly uncertain with only three countries having two repeated national surveys, highlighting the need for further data on this. Additionally, the systematic reviews used for this analysis, although from 2017, lacked data from recent years where HCV outbreaks have occurred driven by IDU in some countries, notably USA(110) where a higher tPAF is estimated when increased numbers of PWID are assumed. The lack of robust data on HCV prevalence, especially for the general population, also raises concerns about whether countries will be able to reliably ascertain their progress towards WHO's HCV elimination targets or develop plans to reach them. This highlights the crucial role of good data for policy making. Importantly, a single inaccurate data point could affect a country's results, implying that careful consideration of the assumptions made are required before using my results to inform policy in specific countries.

Despite the limitations described above, it is also important to note that this paper utilises data from 12 reviews, synthesising data from thousands of studies and accounting for the uncertainty in these estimates in our projections. This will have minimised the data issues as far as is currently possible, with my extensive sensitivity analyses showing that the overall

finding that IDU is an important contributor to the global HCV epidemic is robust despite data uncertainties.

7.4.4. Implications

To my knowledge, this is the first study to fully quantify the future contribution of IDU to the global HCV epidemic. The results show that the elevated risks associated with IDU account for 43% of global HCV infections over the next 12 years; with this figure being even higher in HICs (79%). On average 38% of HCV infections from 2018-2030 are due to IDU in LMICs, such as Pakistan (18%) and India (6%), which were discussed in chapters 4 and 5 and where the contribution is much lower than the global average. This corroborates the findings of those chapters that the HCV epidemics in both settings are generalised and transmission is due to multiple risk factors. This information is primarily useful for policy-makers that are uncertain about the importance of combating the HCV epidemic amongst PWID, especially for meeting the WHO's 2030 elimination targets(403). Indeed, globally, my results suggest the incidence of HCV in PWID needs to be reduced by at least half to have any hope of reducing the overall incidence of HCV by 80%. Such a reduction in incidence can be achieved through reducing prevalence or transmission risks, including via micro elimination initiatives that either scale-up HCV treatment for PWID (investigated in chapter 8) or prevention interventions(211), such as needle and syringe provision (NSP) and opiate substitution therapy (OST) programs. Newly synthesised data and modelling has shown that these interventions can dramatically reduce levels of HCV incidence(110, 287), can be cost-effective in various settings(224, 287), and can also prevent other blood-borne viruses such as HIV(393). However, the current coverage of NSP and OST is low in most countries(209), as is the coverage of direct acting antiviral drug treatment(409), with PWID being frequently denied treatment(313). Barriers restricting the coverage of these interventions to PWID need to be urgently addressed to achieve the WHO HCV elimination targets. In chapter 8 I use the same models covering the 88 countries to look at treatment as prevention for a range of infected subgroups, including PWID.

CHAPTER 8. MODELLING THE POTENTIAL PREVENTION BENEFITS OF A TREAT-ALL HEPATITIS C VIRUS TREATMENT STRATEGY AT GLOBAL-, REGIONAL-, AND COUNTRY-LEVELS: A MODELLING STUDY

The work in this chapter was done in collaboration with Hannah Fraser, Aaron G Lim, Josephine G Walker, Amy Peacock, Samantha Colledge, Janni Leung, Jason Grebely, Sarah Larney, Natasha K Martin, Louisa Degenhardt, Matthew Hickman, Margaret T May, and Peter Vickerman, was commissioned by the World Health Organization and is published in the supplement of the 2018 World Health Organization guidelines on HCV(410) and in the Journal of Viral Hepatitis(374).

8.1. Introduction

Direct-acting antiviral (DAA) treatments have made hepatitis C virus (HCV) an easily curable infection(104). Historically the emphasis was on treating people with advanced liver disease due to the high prices of treatment(397). However, a wider allocation of treatment is required to eliminate HCV. To encourage widespread treatment scale-up, the World Health Organization (WHO) developed HCV treatment guidelines in 2018 advising that countries should allow access to HCV treatment for all infected individuals: a "treat-all" strategy(408). The modelling in this chapter fed into the evidence development for these guidelines.

In chapter 7, I found that around 43% of all transmission globally would be averted between 2018 and 2030 if the additional transmission risks associated with injecting drug use (IDU) were removed, on average 38% in low- and middle-income countries and 79% in high-income countries. This indicates that it will be impossible to achieve the WHO targets for reducing HCV incidence by 80% without countries achieving a large reduction in HCV transmission among PWID, which previous modelling suggests will need a large scale-up in treatment(236, 384). Achieving the WHO targets for incidence will require reductions in incidence in other groups, which will likely require a scale-up in treatment for a wide-range

of populations. However, in many countries people who inject drugs (PWID) are denied HCV treatment and access is prioritised for those with advanced liver disease(409); a situation that would be avoided with a treat-all strategy allowing access to HCV treatment for all individuals that seek it.

A treat-all HCV treatment strategy could also produce clinical benefits, such as reducing the risks of severe liver disease(52). Previous analyses have considered who should be treated to achieve greatest morbidity and mortality benefits(79, 235, 240), whilst other analyses have considered the cost-effectiveness of different treatment strategies(240). However, these analyses have generally used static models so have not included prevention benefits of treatment unless they focussed on PWID, assuming benefits would be negligible when not treating such high-risk groups(34). To help countries and the WHO understand the overall benefits of a treat-all policy, the WHO commissioned this analysis to evaluate the prevention benefits of HCV treatment and determine how country-level demographic and epidemiological differences could affect the prevention benefits achieved.

8.2. Methods

The model structure, parameterisation, and calibration used in this chapter are the same as that described in Chapter 6.

8.2.1. Model analyses

The 1000 full model fits for each country were run over 2018-2038, firstly with that country's baseline level of treatment (counterfactual projections) and then with 50 additional individuals being treated in 2018, with the difference in the number of new infections between the paired runs being divided by 50 to give the infections averted per additional treatment over 20-years. Fifty treatments were chosen to give an estimate of the initial prevention benefit of further treatment scale-up while being small enough not to alter the course of each country's ongoing epidemic trajectory. This number gives an estimate of the initial prevention benefit of further treatment scale-up. The effect of this treatment assumption was investigated in a sensitivity analysis.

I considered several scenarios that assumed the treated individuals were either:

- selected randomly from all infected individuals (treat-all),
- selected from PWID,
- selected from people with cirrhosis,
- selected from people ≥35 years old.

Infected individuals can overlap between categories, so treatment is randomly allocated within the subgroups. For each scenario and country, projections across the 1000 model fits were used to produce 95% credibility intervals (95% CrI) for all impact estimates by taking the 2.5th and 97.5th percentiles of the 1,000 simulated runs, whilst the main estimate is calculated as the median of these runs. For each scenario, regional and global estimates of the infections averted per treatment were produced by weighting country-level estimates by that country's relative burden of HCV compared to the modelled regional and global burdens.

8.2.2. Associations with infections averted per treatment

Univariable and multivariable regression models investigated which country-level characteristics were associated with the number of infections averted per randomly allocated treatment and per treatment among PWID. The country-level characteristics included in these analyses were current population growth rate, population-attributable fraction of IDU to HCV transmission (the percentage of new HCV infections prevented 2018-2038 if the additional transmission risk among PWID was reduced to zero as defined in chapter 7), population percentage of PWID among adults, average duration of IDU, HCV prevalence among PWID and the general population, and the total number of treatments given in 2017.

8.2.3. Sensitivity analyses

Sensitivity analyses were run for 100 complete model runs to save computational time, as the results for 100 and 1,000 runs were similar. Sensitivity analyses considered the effect of specific assumptions in the model: assuming stable HCV epidemics instead of decreasing epidemics, assuming a recent increase in IDU in USA(110) in line with the on-going opioid

epidemic, assuming longer-term epidemics of IDU in Sub-Saharan Africa and Eastern Europe instead of them recently evolving, assuming treatment rates are halved among PWID and doubled among people with cirrhosis (but overall allocating the same number of treatments), assuming HCV epidemic trajectories vary based on regional data, and treating an extra 25 infected individuals instead of 50. I also estimated the prevention impact of on-going levels of treatment in each country, by comparing the impact achieved over 20 years with on-going treatment rates to the impact achieved if the treatments in 2018 had not occurred but treatment levels resumed in subsequent years. Lastly, I examined the infections averted per treatment when only including the 66 countries with ≥2 of the key prevalence parameters scored as moderate or better (table 6.7).

8.3. Results

The results of the model fitting are the same as those presented in section 7.3.1.

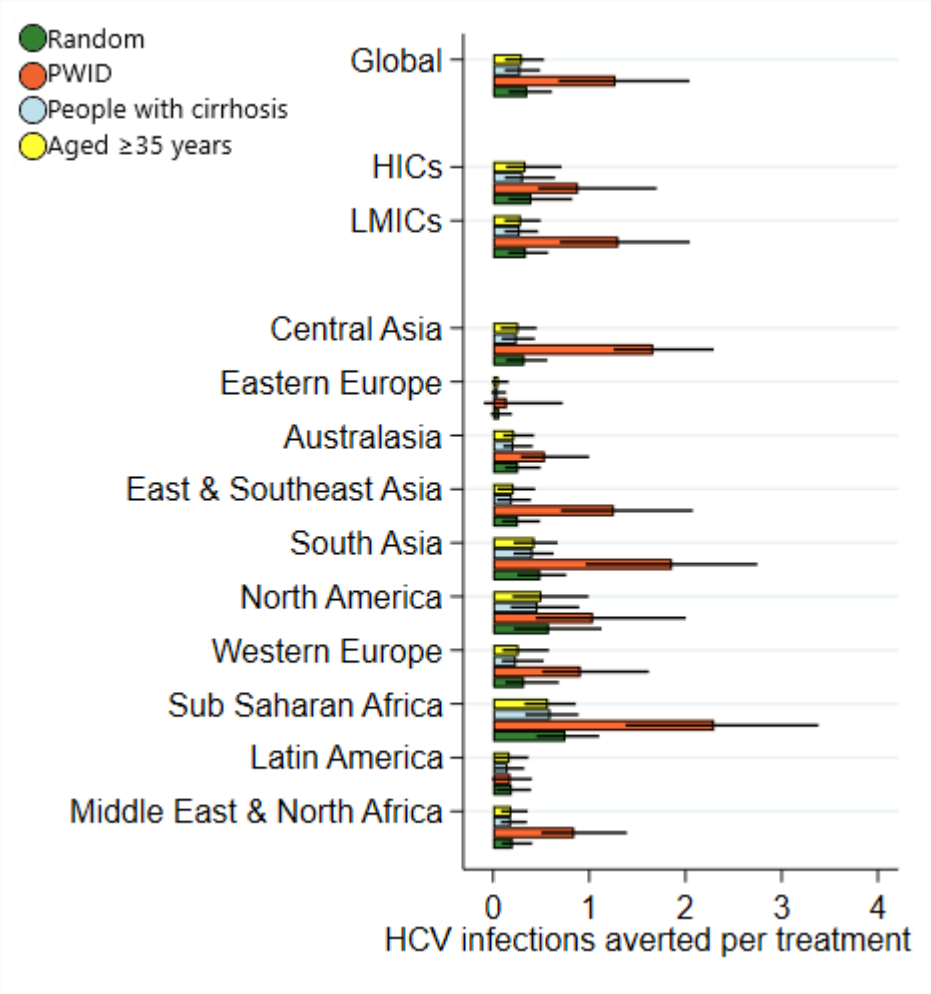
8.3.1. Infections averted per treatment

Globally, the model estimates 0.35 (95% CrI: 0.16, 0.61) infections are averted per treatment over the next 20 years from treating people randomly. China, India, Nigeria, Pakistan, and Russia, which contain around 52% of infected individuals in the modelled countries, drive this global estimate. The estimated infections averted vary substantially across regions and countries (figure 8.1; table 8.1). The region with the lowest infections averted per randomly allocated treatment is Eastern Europe, 0.06 (95% CrI: -0.03, 0.20), while Sub-Saharan Africa has the highest, 0.75 (95% CrI: 0.45, 1.10).

Table 8.1 and figure 8.1 show the prevention benefit of randomly allocating treatment compared to targeting treatment to PWID, patients with cirrhosis, or people aged ≥35. Globally, treating PWID achieves the most prevention impact with 1.27 (95% CrI: 0.68, 2.04) infections averted per treatment. This ranges from as much as 4.82 (95% CrI: 1.98, 6.86) in Madagascar, to negative in Mauritius [–0.52 (95% CrI: –0.60, –0.14)] due to high levels of re-infection of PWID, although overall numbers of infected individuals still reduce because of the additional individuals cured through treatment. Globally, the infections averted per treatment given to individuals with cirrhosis [0.28 (95% CrI: 0.12, 0.49)] or individuals aged

≥35 years [0.30 (95% CrI: 0.12, 0.53)] is less but similar to what is achieved from randomly allocating treatment. Figure 8.2 shows that for the 88 countries modelled there is a strong positive linear trend between the infections averted per randomly allocated treatment and the infections averted per treatment targeted to PWID.

Figure 8.1: Chronic HCV infections averted per HCV treatment (2018-2038) globally, by country income level and by region; stratified by allocation strategy*.



HICs: High-income countries; LMICs: Low- and middle-income countries

* Whiskers are 95% credibility intervals.

Table 8.1: The number of chronic HCV infections averted per treatment over 2018-2038 for the different treatment allocation scenarios, for each country, region, and globally.

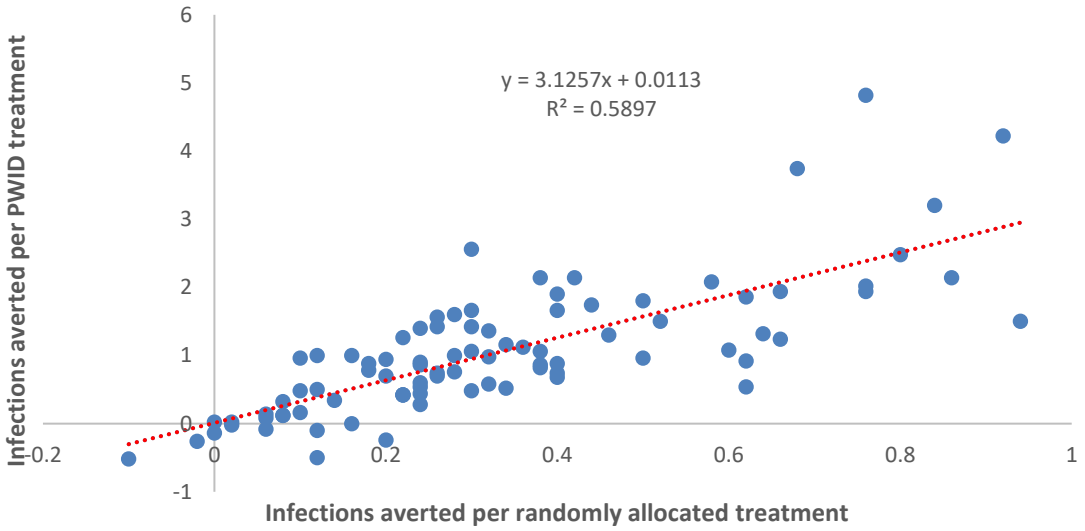
Country	Chronic hepatitis C virus infections averted per treatment for different allocation strategies (95% credibility intervals)			
	Random (treat-all)	PWID*	People with cirrhosis	People aged ≥35 years
Global	**0.35 (0.16, 0.61)**	**1.27 (0.68, 2.04)**	**0.28 (0.12, 0.49)**	**0.30 (0.12, 0.53)**
Central Asia	**0.32 (0.14, 0.56)**	**1.66 (1.25, 2.29)**	**0.24 (0.09, 0.43)**	**0.26 (0.08, 0.45)**
Kazakhstan	0.26 (0.18, 0.40)	1.42 (1.08, 2.38)	0.14 (0.08, 0.26)	0.16 (0.08, 0.28)
Kyrgyzstan	0.42 (0.24, 0.62)	2.14 (1.66, 2.78)	0.30 (0.12, 0.48)	0.30 (0.12, 0.48)
Tajikistan	0.50 (0.24, 0.76)	1.80 (1.36, 2.32)	0.38 (0.14, 0.60)	0.38 (0.14, 0.60)
Turkmenistan	0.40 (0.20, 0.64)	1.66 (1.10, 2.40)	0.30 (0.12, 0.50)	0.32 (0.14, 0.54)
Uzbekistan	0.30 (0.10, 0.56)	1.66 (1.26, 2.22)	0.24 (0.08, 0.44)	0.26 (0.06, 0.46)
Eastern Europe	**0.06 (-0.03, 0.20)**	**0.14 (-0.10, 0.72)**	**0.05 (-0.02, 0.14)**	**0.06 (-0.02, 0.16)**
Armenia	0.12 (0.02, 0.26)	0.50 (0.12, 1.02)	0.08 (0.02, 0.20)	0.08 (0.02, 0.22)
Azerbaijan	0.24 (0.06, 0.46)	0.28 (-0.08, 0.76)	0.20 (0.06, 0.38)	0.22 (0.06, 0.44)
Belarus	0.00 (-0.10, 0.14)	-0.14 (-0.36, 0.34)	0.00 (-0.06, 0.12)	0.00 (-0.06, 0.14)
Bosnia	0.00 (-0.12, 0.14)	0.02 (-0.18, 0.32)	0.00 (-0.10, 0.08)	0.00 (-0.10, 0.10)
Bulgaria	0.02 (-0.04, 0.10)	-0.02 (-0.20, 0.50)	0.00 (-0.02, 0.10)	0.02 (-0.02, 0.12)
Czechia	0.80 (0.54, 1.46)	2.48 (1.90, 3.24)	0.50 (0.28, 1.02)	0.60 (0.36, 1.20)
Estonia	0.40 (0.08, 0.80)	0.68 (0.08, 1.48)	0.28 (0.06, 0.62)	0.32 (0.08, 0.70)
Georgia	0.40 (0.14, 0.72)	0.74 (0.48, 1.06)	0.32 (0.12, 0.58)	0.34 (0.12, 0.62)
Hungary	0.20 (0.06, 0.42)	0.94 (0.40, 1.68)	0.16 (0.04, 0.36)	0.18 (0.04, 0.38)
Latvia	0.06 (-0.06, 0.26)	0.08 (-0.20, 0.70)	0.04 (-0.04, 0.18)	0.06 (-0.04, 0.20)
Lithuania	0.18 (0.08, 0.36)	0.88 (0.62, 1.30)	0.14 (0.06, 0.30)	0.16 (0.06, 0.32)
Moldova	0.14 (0.02, 0.30)	0.34 (-0.04, 0.88)	0.10 (0.00, 0.24)	0.12 (0.00, 0.28)
Poland	0.10 (0.00, 0.26)	0.16 (-0.02, 0.38)	0.08 (0.00, 0.22)	0.10 (0.00, 0.26)
Romania	-0.02 (-0.08, 0.06)	-0.26 (-0.38, 0.24)	0.00 (-0.06, 0.06)	0.00 (-0.06, 0.08)
Russia	0.02 (-0.06, 0.14)	0.02 (-0.22, 0.66)	0.02 (-0.04, 0.08)	0.02 (-0.04, 0.10)
Slovakia	0.08 (-0.06, 0.28)	0.12 (-0.24, 0.70)	0.04 (-0.04, 0.20)	0.06 (-0.04, 0.24)
Ukraine	0.10 (0.06, 0.22)	0.48 (0.30, 1.02)	0.06 (0.02, 0.16)	0.08 (0.04, 0.18)

	Chronic hepatitis C virus infections averted per treatment for different allocation strategies (95% credibility intervals)			
	Random (treat-all)	**PWID***	**People with cirrhosis**	**People aged ≥35 years**
Australasia	**0.26 (0.13, 0.49)**	**0.54 (0.29, 1.00)**	**0.21 (0.11, 0.41)**	**0.22 (0.11, 0.43)**
Australia	0.24 (0.14, 0.40)	0.54 (0.34, 0.92)	0.20 (0.12, 0.34)	0.20 (0.12, 0.34)
New Zealand	0.34 (0.06, 0.90)	0.52 (0.06, 1.34)	0.26 (0.04, 0.72)	0.30 (0.04, 0.80)
East & Southeast Asia	**0.26 (0.09, 0.49)**	**1.26 (0.70, 2.08)**	**0.19 (0.04, 0.39)**	**0.21 (0.04, 0.44)**
China	0.24 (0.10, 0.44)	1.40 (0.82, 2.26)	0.18 (0.04, 0.36)	0.20 (0.04, 0.40)
Indonesia	0.12 (-0.04, 0.36)	-0.10 (-0.26, 0.10)	0.12 (-0.02, 0.30)	0.12 (-0.02, 0.34)
Japan	0.46 (0.18, 0.88)	1.30 (0.68, 2.18)	0.32 (0.10, 0.66)	0.36 (0.12, 0.72)
Malaysia	0.32 (0.10, 0.56)	0.58 (0.26, 0.94)	0.26 (0.06, 0.46)	0.28 (0.08, 0.52)
Myanmar	0.30 (0.18, 0.50)	2.56 (1.96, 3.88)	0.18 (0.06, 0.34)	0.18 (0.06, 0.38)
Philippines	0.38 (0.16, 0.64)	2.14 (1.14, 3.68)	0.30 (0.12, 0.52)	0.34 (0.14, 0.56)
Taiwan	0.06 (-0.02, 0.26)	-0.08 (-0.24, 0.14)	0.06 (-0.02, 0.22)	0.06 (0.00, 0.26)
Thailand	0.16 (0.00, 0.38)	0.00 (-0.18, 0.22)	0.14 (0.00, 0.32)	0.16 (0.00, 0.36)
Viet Nam	0.24 (0.06, 0.44)	0.90 (0.40, 1.58)	0.18 (0.02, 0.34)	0.20 (0.02, 0.38)
South Asia	**0.49 (0.25, 0.76)**	**1.86 (0.96, 2.75)**	**0.41 (0.21, 0.63)**	**0.43 (0.21, 0.67)**
Afghanistan	0.86 (0.34, 1.34)	2.14 (1.16, 3.36)	0.62 (0.16, 1.02)	0.66 (0.18, 1.02)
Bangladesh	0.40 (0.20, 0.66)	1.90 (1.14, 2.92)	0.32 (0.16, 0.54)	0.34 (0.16, 0.56)
India	0.44 (0.22, 0.70)	1.74 (1.26, 2.48)	0.38 (0.20, 0.58)	0.40 (0.20, 0.64)
Iran	0.32 (0.10, 0.64)	0.98 (0.38, 1.86)	0.22 (0.04, 0.46)	0.26 (0.06, 0.52)
Nepal	0.30 (0.08, 0.56)	1.06 (0.46, 1.94)	0.22 (0.02, 0.42)	0.24 (0.04, 0.46)
Pakistan	0.58 (0.32, 0.86)	2.08 (0.50, 3.14)	0.48 (0.26, 0.72)	0.50 (0.26, 0.74)
North America	**0.58 (0.22, 1.13)**	**1.04 (0.44, 2.00)**	**0.46 (0.18, 0.90)**	**0.50 (0.20, 0.99)**
Canada	0.30 (-0.06, 0.72)	0.48 (-0.28, 1.28)	0.24 (-0.04, 0.58)	0.26 (-0.04, 0.64)
USA	0.60 (0.24, 1.16)	1.08 (0.50, 2.06)	0.48 (0.20, 0.92)	0.52 (0.22, 1.02)
Western Europe	**0.32 (0.13, 0.68)**	**0.91 (0.51, 1.62)**	**0.24 (0.09, 0.53)**	**0.27 (0.1, 0.58)**
Albania	0.10 (0.04, 0.24)	0.96 (0.72, 1.36)	0.08 (0.02, 0.18)	0.08 (0.02, 0.20)
Austria	0.66 (0.38, 1.08)	1.24 (0.72, 1.94)	0.50 (0.26, 0.84)	0.56 (0.28, 0.94)
Belgium	0.26 (0.06, 0.70)	0.74 (0.20, 1.36)	0.18 (0.02, 0.54)	0.20 (0.04, 0.60)
Croatia	0.16 (0.06, 0.32)	1.00 (0.70, 1.44)	0.10 (0.04, 0.24)	0.12 (0.04, 0.26)
Cyprus	0.32 (0.10, 0.56)	1.36 (0.88, 1.96)	0.24 (0.06, 0.44)	0.28 (0.08, 0.50)

	Chronic hepatitis C virus infections averted per treatment for different allocation strategies (95% credibility intervals)			
	Random (treat-all)	**PWID***	**People with cirrhosis**	**People aged ≥35 years**
Denmark	0.38 (0.28, 0.52)	1.06 (0.80, 1.42)	0.26 (0.16, 0.40)	0.30 (0.20, 0.46)
Finland	0.06 (-0.02, 0.16)	0.14 (-0.04, 0.68)	0.04 (-0.02, 0.10)	0.04 (0.00, 0.12)
France	0.28 (0.14, 0.60)	0.76 (0.46, 1.40)	0.22 (0.12, 0.46)	0.24 (0.12, 0.50)
Germany	0.40 (0.18, 0.80)	0.88 (0.54, 1.38)	0.30 (0.12, 0.62)	0.34 (0.14, 0.70)
Greece	0.22 (0.04, 0.42)	0.42 (0.20, 0.70)	0.18 (0.04, 0.34)	0.20 (0.04, 0.40)
Iceland	0.26 (0.18, 0.38)	0.70 (0.44, 1.16)	0.18 (0.14, 0.26)	0.20 (0.14, 0.28)
Ireland	0.22 (0.06, 0.44)	0.42 (0.14, 0.80)	0.18 (0.04, 0.36)	0.20 (0.04, 0.40)
Italy	0.24 (0.08, 0.50)	0.86 (0.54, 1.60)	0.16 (0.06, 0.36)	0.18 (0.06, 0.40)
Luxembourg	0.94 (0.28, 1.60)	1.50 (0.54, 2.52)	0.76 (0.22, 1.30)	0.82 (0.24, 1.38)
Macedonia	0.08 (0.04, 0.22)	0.32 (0.20, 0.48)	0.04 (0.02, 0.18)	0.06 (0.02, 0.20)
Malta	0.36 (0.20, 0.64)	1.12 (0.60, 2.18)	0.28 (0.16, 0.48)	0.32 (0.18, 0.54)
Montenegro	0.12 (0.08, 0.22)	1.00 (0.70, 2.00)	0.06 (0.04, 0.14)	0.06 (0.04, 0.16)
Netherlands	0.28 (0.12, 0.58)	1.00 (0.38, 1.76)	0.24 (0.10, 0.48)	0.26 (0.10, 0.52)
Norway	0.64 (0.40, 0.94)	1.32 (0.90, 1.82)	0.50 (0.28, 0.74)	0.56 (0.32, 0.82)
Portugal	0.24 (0.06, 0.46)	0.44 (-0.14, 0.80)	0.20 (0.06, 0.40)	0.22 (0.06, 0.42)
Serbia	0.30 (0.22, 0.38)	1.42 (1.12, 2.20)	0.14 (0.10, 0.20)	0.18 (0.12, 0.24)
Slovenia	0.52 (0.38, 0.74)	1.50 (1.14, 2.18)	0.36 (0.24, 0.54)	0.42 (0.28, 0.62)
Spain	0.20 (0.08, 0.50)	0.70 (0.38, 1.12)	0.18 (0.06, 0.44)	0.20 (0.06, 0.46)
Sweden	0.62 (0.10, 1.18)	0.92 (0.00, 1.52)	0.52 (0.08, 1.00)	0.56 (0.10, 1.08)
Switzerland	0.38 (0.18, 0.64)	0.86 (0.52, 1.32)	0.30 (0.16, 0.52)	0.34 (0.16, 0.56)
UK	0.50 (0.22, 1.22)	0.96 (0.38, 2.04)	0.36 (0.14, 0.94)	0.40 (0.16, 1.04)
Sub-Saharan Africa	**0.75 (0.45, 1.10)**	**2.30 (1.38, 3.38)**	**0.60 (0.33, 0.89)**	**0.57 (0.33, 0.86)**
Ghana	0.66 (0.40, 0.98)	1.94 (1.40, 2.64)	0.54 (0.32, 0.80)	0.54 (0.34, 0.80)
Kenya	0.68 (0.38, 1.04)	3.74 (2.22, 5.82)	0.50 (0.26, 0.80)	0.48 (0.26, 0.76)
Madagascar	0.76 (0.44, 1.16)	4.82 (1.98, 6.86)	0.60 (0.34, 0.94)	0.62 (0.36, 0.94)
Mauritius	-0.10 (-0.26, 0.10)	-0.52 (-0.60, -0.14)	-0.06 (-0.18, 0.12)	-0.04 (-0.18, 0.14)
Mozambique	0.62 (0.28, 0.96)	0.54 (0.20, 1.00)	0.50 (0.22, 0.80)	0.44 (0.20, 0.72)
Nigeria	0.76 (0.46, 1.12)	2.02 (1.04, 3.18)	0.62 (0.38, 0.92)	0.60 (0.36, 0.88)
Senegal	0.76 (0.46, 1.14)	1.94 (1.16, 2.98)	0.62 (0.38, 0.94)	0.62 (0.38, 0.90)

	Chronic hepatitis C virus infections averted per treatment for different allocation strategies (95% credibility intervals)			
	Random (treat-all)	**PWID***	**People with cirrhosis**	**People aged ≥35 years**
Tanzania	0.84 (0.54, 1.18)	3.20 (2.34, 4.26)	0.62 (0.30, 0.90)	0.58 (0.30, 0.90)
Latin America	**0.19 (0.03, 0.40)**	**0.18 (-0.01, 0.40)**	**0.15 (0.02, 0.32)**	**0.17 (0.02, 0.37)**
Argentina	0.24 (0.06, 0.46)	0.60 (0.36, 0.90)	0.18 (0.04, 0.36)	0.22 (0.04, 0.42)
Brazil	0.22 (0.08, 0.40)	0.42 (0.20, 0.68)	0.16 (0.04, 0.32)	0.18 (0.04, 0.36)
Mexico	0.12 (-0.08, 0.36)	-0.50 (-0.60, -0.38)	0.12 (-0.04, 0.32)	0.14 (-0.04, 0.36)
Uruguay	0.28 (0.12, 0.46)	1.60 (1.16, 2.28)	0.20 (0.06, 0.34)	0.22 (0.08, 0.40)
Middle East & North Africa	**0.20 (0.09, 0.41)**	**0.84 (0.50, 1.39)**	**0.18 (0.08, 0.35)**	**0.19 (0.08, 0.36)**
Egypt	0.18 (0.08, 0.38)	0.78 (0.46, 1.26)	0.18 (0.08, 0.34)	0.18 (0.08, 0.34)
Israel	0.62 (0.38, 0.88)	1.86 (1.40, 2.42)	0.48 (0.28, 0.70)	0.54 (0.32, 0.78)
Lebanon	0.92 (0.58, 1.44)	4.22 (3.14, 6.14)	0.66 (0.36, 1.04)	0.74 (0.42, 1.16)
Libya	0.20 (0.00, 0.42)	-0.24 (-0.38, -0.06)	0.18 (0.02, 0.36)	0.20 (0.02, 0.40)
Morocco	0.34 (0.16, 0.54)	1.16 (0.54, 1.84)	0.28 (0.12, 0.46)	0.30 (0.14, 0.48)
Saudi Arabia	0.08 (-0.02, 0.40)	0.12 (-0.08, 0.46)	0.08 (-0.02, 0.34)	0.08 (-0.02, 0.38)
Syria	0.38 (0.18, 0.66)	0.82 (0.20, 1.70)	0.32 (0.14, 0.54)	0.34 (0.16, 0.56)
Tunisia	0.26 (0.12, 0.50)	1.56 (1.20, 2.08)	0.16 (0.04, 0.34)	0.18 (0.06, 0.40)
Turkey	0.22 (0.12, 0.42)	1.26 (0.92, 2.32)	0.10 (0.04, 0.30)	0.12 (0.04, 0.34)

Figure 8.2: Scatter plot of the infections averted per randomly allocated treatment against the infections averted per treatment allocated to PWID, both for 2018-2038.



8.3.2. Determinants of impact

The infections averted per randomly allocated treatment (table 8.2) is positively associated with a country's population growth-rate [multivariable regression coefficient: 0.12 (95% Confidence interval [CI]: 0.08, 0.17)], with the univariable association seen in figure 8.3a. The infections averted per randomly allocated treatment is also positively associated with the percentage of adults that are PWID [coefficient: 0.14 (95% CI: 0.03, 0.24)] (figure 8.3b shows the univariable association), whereas it is negatively associated with the HCV prevalence in the general population [coefficient: -0.09 (95% CI: -0.15, -0.02)] figure 8.3c, univariable) and PWID [coefficient: -0.006 (95% CI: -0.009, -0.003)] (figure 8.3d, univariable). The multivariable regression model's R^2-value is 0.58, indicating these variables explain most of the variation in estimated infections averted between countries.

Similarly, the number of infections averted per treatment allocated to PWID was positively associated with a country's population growth-rate (figure 8.4a shows the univariable association) [multivariable coefficient: 0.20 (95% CI: 0.07, 0.33)] and the percentage of adults that are PWID [coefficient: 0.32 (95% CI: 0.00, 0.64)] (figure 8.4b, univariable). It was negatively associated with the prevalence of HCV among the general population [coefficient: -0.23 (95% CI: -0.42, -0.03)] (figure 8.4c, univariable) and among PWID [coefficient: -0.047 (95% CI: -0.056, -0.039)] (figure 8.4d, univariable). The R^2-value for this

multivariable model was 0.77. Allocating treatment to PWID resulted in negative infections averted in eight (8%) countries that had high (≥61%) chronic HCV prevalence among PWID, which resulted in high modelled re-infection rates.

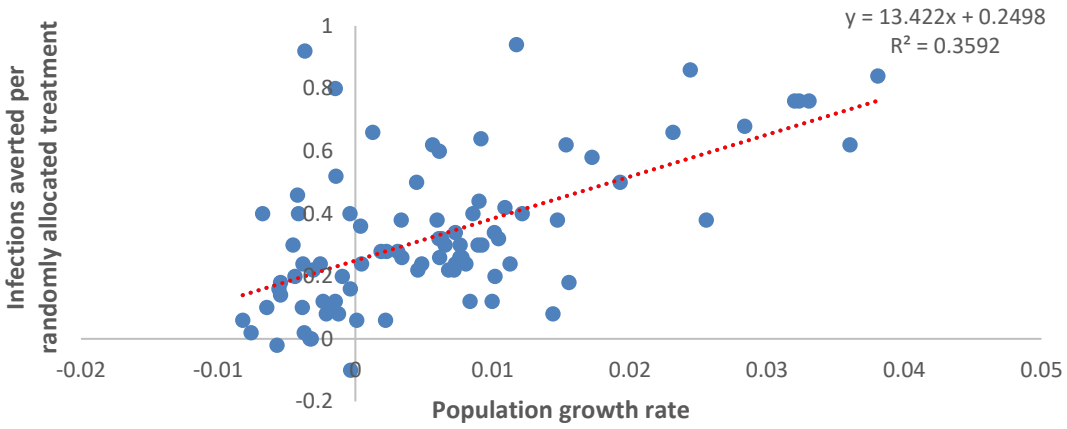
Table 8.2: Univariable and multivariable regression coefficients, showing associations between demographic and epidemiological variables and (a) the number of infections averted per randomly allocated treatment, and (b) the number of infections averted per treatment allocated to PWID.

Variable	Mean (Range) across country-level variable	Infections averted per randomly allocated treatment			
		Univariable regression coefficient (95% CI)	P-value	Multivariable regression coefficient (95% CI)	P-value
Population growth rate (% increase in population per	0.6% (-0.8%, 3.8%)	0.13 (0.10, 0.17)	<0.001	0.12 (0.08, 0.17)	<0.001
General population chronic HCV prevalence (%)*	1.1% (0.1%, 6.0%)	-0.03 (-0.08, 0.03)	0.332	-0.09 (-0.15, -0.02)	0.008
PWID chronic HCV prevalence (%)*	37.2% (3.9%, 72.7%)	-0.009 (-0.012, -0.006)	<0.001	-0.006 (-0.009, -0.003)	<0.001
Percentage of adults that are PWID*	0.44% (0.02%, 3.95%)	-0.00 (-0.10, 0.10)	0.998	0.14 (0.03, 0.24)	0.010
Population attributable fraction of HCV due to IDU*	68.9% (1.6%, 100.0%)	-0.003 (-0.004, -0.001)	0.001	-0.001 (-0.003, 0.001)	0.378
Injecting duration (years)**	13.1 (4.4, 24.8)	-0.01 (-0.02, 0.00)	0.196	0.01 (-0.00, 0.01)	0.144
Number of treatments given in 2017	17,274 (0, 600,000)	0.00 (0.00, 0.00)	0.987	0.00 (0.00, 0.00)	0.330
		Infections averted per PWID allocated treatment			
Population growth rate (% increase in population per	0.6% (-0.8%, 3.8%)	0.46 (0.29, 0.63)	<0.001	0.20 (0.07, 0.33)	0.004
General population chronic HCV prevalence (%)*	1.1% (0.1%, 6.0%)	-0.07 (-0.28, 0.14)	0.499	-0.23 (-0.42, -0.03)	0.024
PWID antibody HCV prevalence (%)*	37.2% (3.9%, 72.7%)	-0.058 (-0.067, -0.049)	<0.001	-0.047 (-0.056, -0.039)	<0.001
Percentage of adults that are PWID*	0.44% (0.02%, 3.95%)	-0.14 (-0.53, 0.25)	0.471	0.32 (0.00, 0.64)	0.048
Population attributable fraction of HCV due to IDU*	68.9% (1.6%, 100.0%)	-0.014 (-0.020, -0.008)	<0.001	-0.005 (-0.011, 0.000)	0.070
Injecting duration (years)**	13.1 (4.4, 24.8)	-0.08 (-0.12, -0.04)	<0.001	-0.02 (-0.05, 0.00)	0.077
Number of treatments given in 2017	17,274 (0, 600,000)	0.00 (0.00, 0.00)	0.991	0.00 (0.00, 0.00)	0.730

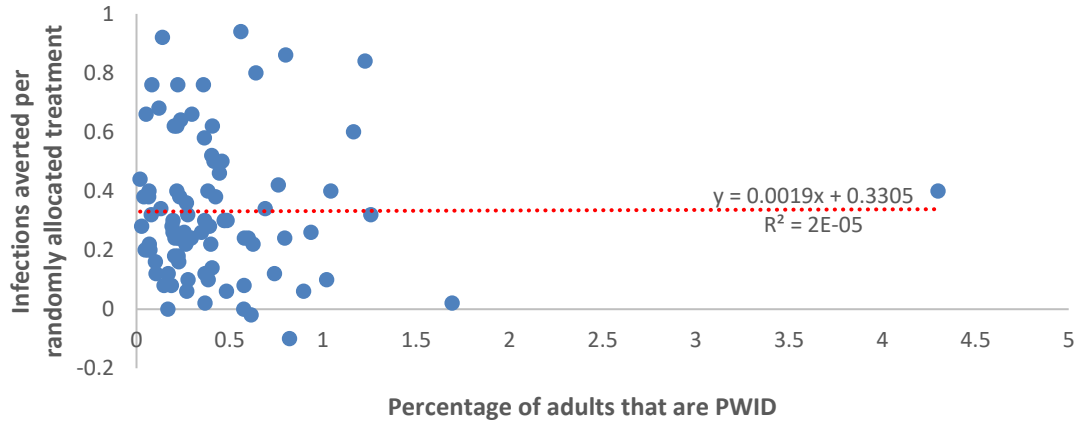
* Per percentage point increase; ** per year of injecting duration

Figure 8.3: Scatter plots of the univariable associations between the number of HCV infections averted (2018-2038) per treatment given randomly against country-level variables:

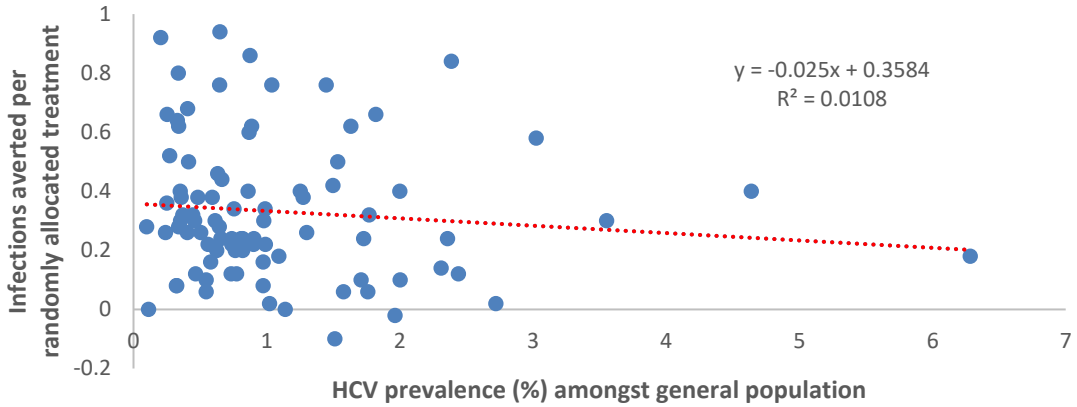
a) A country's population growth rate.



b) The percentage of adults that are PWID in 2015.



c) The HCV prevalence among the general population in 2015.



d) The HCV prevalence among PWID in 2015.

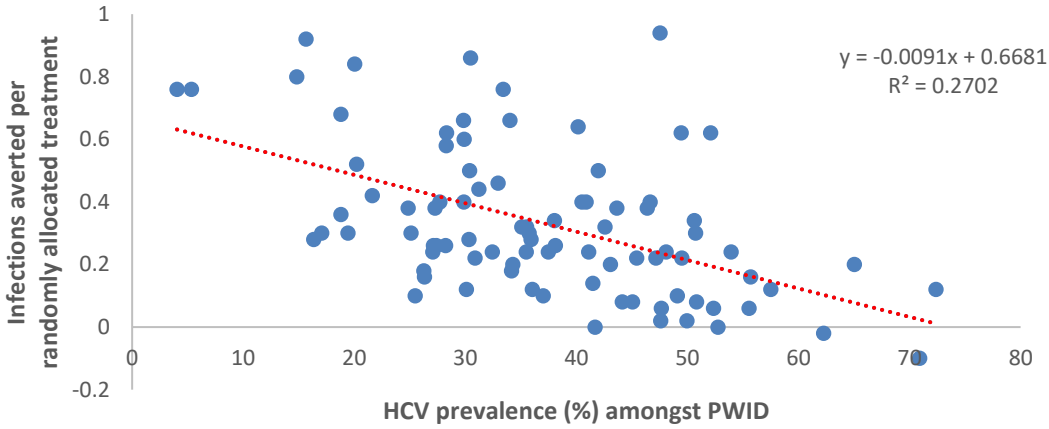
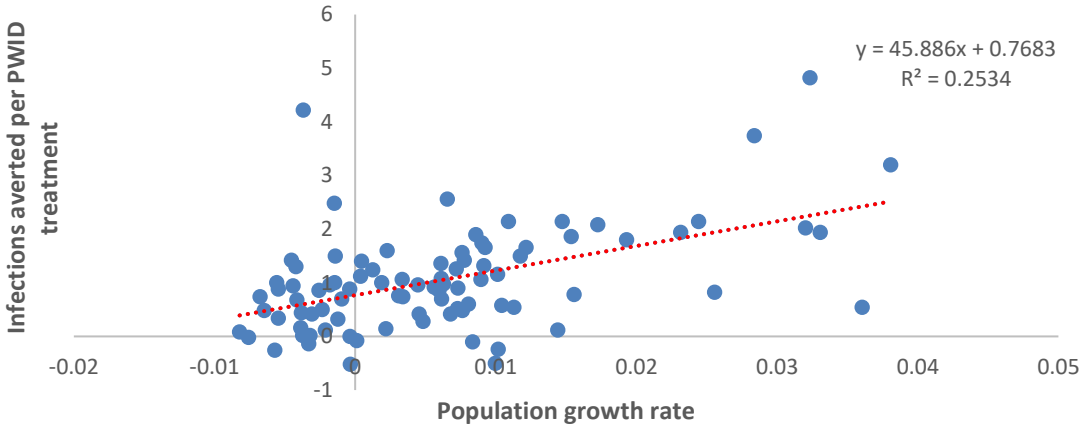
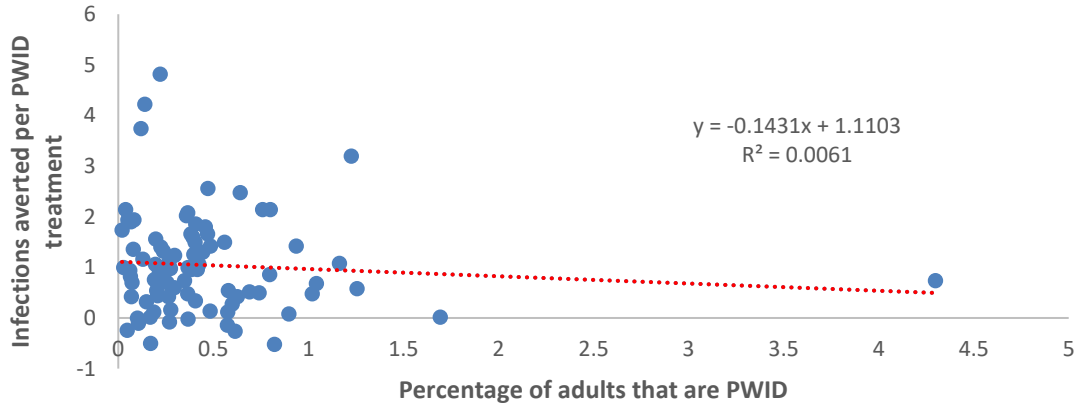


Figure 8.4: Scatter plots of the univariable associations between the number of HCV infections averted (2018-2038) per treatment given to PWID, against country-level variables:

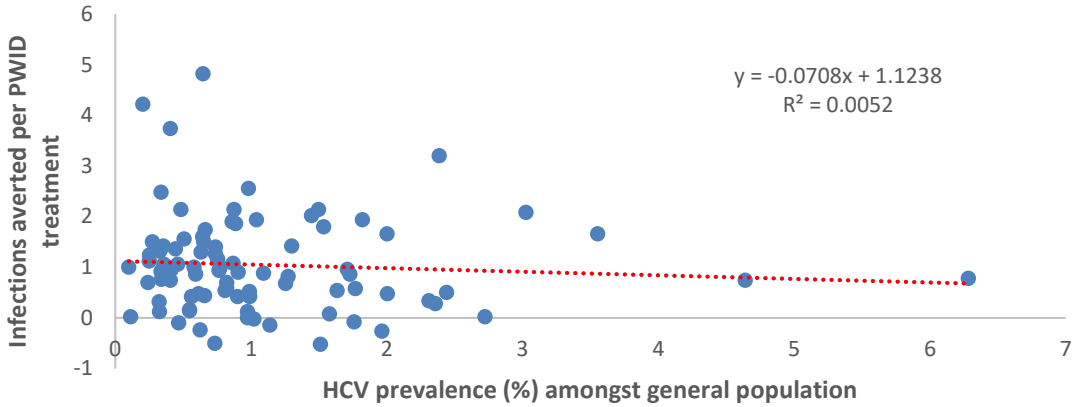
a) A country's population growth rate.



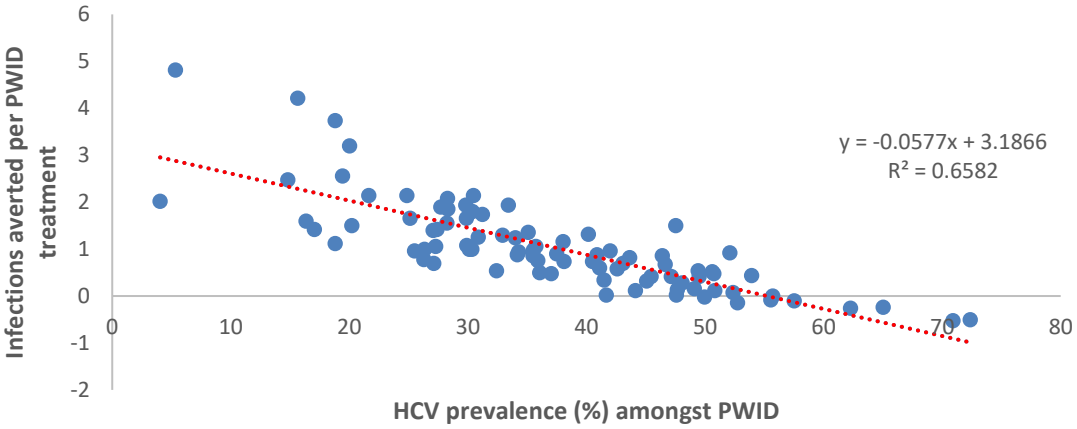
b) The percentage of adults that are PWID in 2015.



c) The HCV prevalence among the general population in 2015.



d) The HCV prevalence among PWID in 2015.



8.3.3. Sensitivity analyses

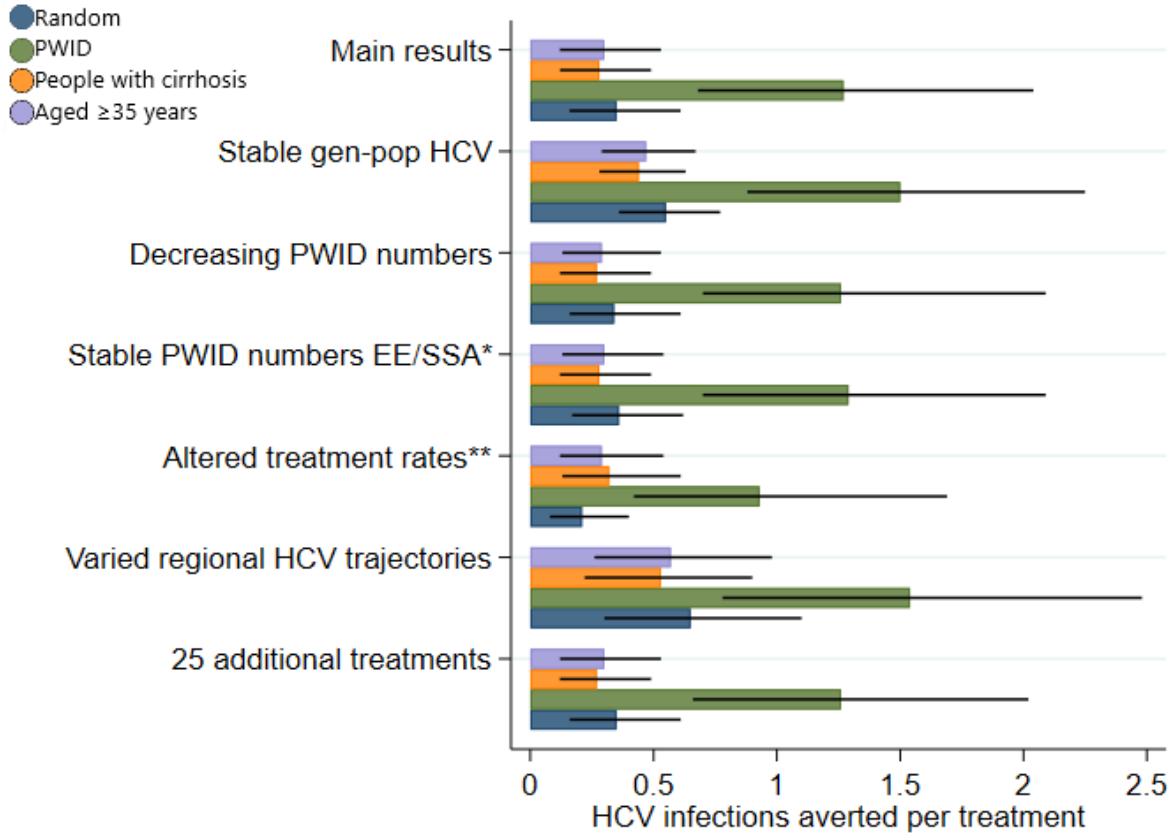
Sensitivity analyses (figure 8.5 and tables 8.3 and 8.4) show each strategy averts more infections if the general population HCV prevalence in each country is stable [0.55 (95% CrI: 0.36, 0.77) infections averted per treatment with random allocation] instead of decreasing as in the baseline projections. The global infections averted per randomly allocated treatment increases to 0.65 (95% CrI: 0.30, 1.10) when assuming different regional epidemic trajectories (see table 6.6). The regions most affected by this change are Central Asia, Eastern Europe, and South Asia, where the infections averted per randomly allocated treatment increase from 0.32 (95% CrI: 0.14, 0.56) to 1.40 (95% CrI: -0.33, 2.19), 0.06 (95% CrI: -0.03, 0.20) to 0.60 (95% CrI: 0.08, 2.21), and 0.49 (95% CrI: 0.25, 0.76) to 0.87 (95% CrI: 0.66, 1.10), respectively.

In the sensitivity analysis where background treatment rates are halved among PWID and doubled for people with cirrhosis this reduces the infections averted per extra randomly allocated treatment by around a third to 0.21 (95% CrI: 0.08, 0.40) compared with the baseline projections. There are more infections averted per randomly allocated treatment when assuming increasing IDU in the USA since 2010(110) [1.02 (95% CrI: 0.30, 2.26) vs 0.60 (95% CrI: 0.24, 1.16) with a stable proportion of PWID]. Assuming either a decreasing HCV epidemic among PWID [0.34 (95% CrI: 0.16, 0.61)] or stable populations of PWID in Eastern Europe and Sub-Saharan Africa [0.36 (95% CrI: 0.17, 0.62)] does not much alter the infections averted per random treatment, globally, nor does giving an additional 25 treatments rather than 50 [0.35 (95% CrI: 0.16, 0.61)]

Table 8.5 gives the projected number of infections averted from ongoing treatment rates in 2018 (around 1.5 million globally) compared to if no treatments were given in 2018 but resumed in 2019. This suggests 525,764 (95% CrI: 243,948, 980,523) chronic HCV infections would be averted over the next 20 years, with similar number of infections averted per treatment for each country and globally [0.34 (95% CrI: 0.16, 0.63)] as previously estimated for the baseline scenario with 50 additional randomly allocated treatments in 2017.

When only including the countries with ≥2 key prevalence parameters having a data quality score of moderate or better, the infections averted per randomly allocated treatment was similar [0.35 (95% CI: 0.15, 0.60)] to the projections that included all countries.

Figure 8.5: Sensitivity analyses for the number of chronic HCV infections averted per treatment over 20 years (2018-2038) for the different treatment allocation scenarios, globally†.



EE: Eastern Europe; SSA: Sub-Saharan Africa

* Eastern Europe and Sub-Saharan Africa seeded at 101% of the estimate of the proportion of adults that are PWID – the same as the other regions.

** The same number of treatments are given as in the main analyses but the treatment rate for PWID is halved, whilst the treatment rate for people with cirrhosis is doubled. The treatment rate for those who are neither PWID nor have cirrhosis is also altered and is either increased or decreased depending on the epidemic.

† Sensitivity analyses were run for 100 complete model runs to save computational time, as the results for 100 and 1,000 runs were similar. Whiskers are 95% credibility intervals.

Table 8.3: Sensitivity analyses for the number of chronic hepatitis C virus infections averted per treatment (2018-2038) for the different treatment allocation scenarios, for each region and globally*.

	Hepatitis C virus infections averted per treatment for infected individuals (95% CrI)			
	Random allocation	**PWID**	**Cirrhotic**	**Age ≥35 years**
Analysis	**Global**			
Main	0.35 (0.16, 0.61)	1.27 (0.68, 2.04)	0.28 (0.12, 0.49)	0.30 (0.12, 0.53)
Stable gen-pop HCV†	0.55 (0.36, 0.77)	1.50 (0.88, 2.25)	0.44 (0.28, 0.63)	0.47 (0.29, 0.67)
Decreasing HCV among PWID§	0.34 (0.16, 0.61)	1.26 (0.70, 2.09)	0.27 (0.12, 0.49)	0.29 (0.13, 0.53)
No later injecting start year for EE and SSA¶	0.36 (0.17, 0.62)	1.29 (0.72, 2.09)	0.28 (0.12, 0.49)	0.30 (0.13, 0.54)
Halved PWID treatment rate, doubled for cirrhosis₡	0.21 (0.08, 0.40)	0.93 (0.42, 1.69)	0.32 (0.13, 0.61)	0.29 (0.12, 0.54)
Varied epidemic trajectories by region	0.65 (0.30, 1.10)	1.54 (0.78, 2.48)	0.53 (0.22, 0.90)	0.57 (0.26, 0.98)
25 additional treatments (rather than 50)	0.35 (0.16, 0.61)	1.26 (0.66, 2.02)	0.27 (0.12, 0.49)	0.30 (0.12, 0.53)
Analysis	**Central Asia**			
Main	0.32 (0.14, 0.56)	1.66 (1.25, 2.29)	0.24 (0.09, 0.43)	0.26 (0.08, 0.45)
Stable gen-pop HCV†	0.54 (0.39, 0.69)	1.85 (1.40, 2.36)	0.42 (0.29, 0.57)	0.43 (0.30, 0.59)
Decreasing HCV among PWID§	0.33 (0.16, 0.57)	1.73 (1.34, 2.35)	0.25 (0.09, 0.45)	0.26 (0.09, 0.47)
Halved PWID treatment rate, doubled for cirrhosis₡	0.18 (0.05, 0.36)	1.42 (1.09, 2.02)	0.28 (0.09, 0.54)	0.25 (0.09, 0.47)
Varied epidemic trajectories by region	1.40 (-0.33, 2.19)	1.89 (-0.14, 3.18)	1.15 (-0.36, 1.81)	1.25 (-0.29, 1.99)
25 additional treatments (rather than 50)	0.31 (0.16, 0.53)	1.65 (1.21, 2.28)	0.24 (0.10, 0.43)	0.25 (0.10, 0.47)
Analysis	**Eastern Europe**			
Main	0.06 (-0.03, 0.20)	0.14 (-0.10, 0.72)	0.05 (-0.02, 0.14)	0.06 (-0.02, 0.16)
Stable gen-pop HCV†	0.13 (0.01, 0.27)	0.16 (0.16, 0.63)	0.10 (0.10, 0.22)	0.12 (0.12, 0.25)
Decreasing HCV among PWID§	0.06 (-0.02, 0.18)	0.14 (-0.09, 0.75)	0.05 (-0.01, 0.15)	0.06 (-0.01, 0.16)
No later injecting start year for EE and SSA¶	0.11 (0.03, 0.21)	0.48 (0.12, 0.89)	0.07 (0.01, 0.14)	0.08 (0.03, 0.16)
Halved PWID treatment rate, doubled for cirrhosis₡	0.02 (0.00, 0.10)	0.05 (-0.20, 0.68)	0.03 (0.01, 0.18)	0.05 (-0.02, 0.17)
Varied epidemic trajectories by region	0.60 (0.08, 2.21)	0.58 (0.04, 1.77)	0.50 (0.06, 1.85)	0.58 (0.08, 2.13)
25 additional treatments (rather than 50)	0.07 (-0.04, 0.21)	0.12 (-0.12, 0.74)	0.04 (-0.02, 0.14)	0.04 (-0.02, 0.17)

	Hepatitis C virus infections averted per treatment for infected individuals			
	Random allocation	**PWID**	**Cirrhotic**	**Age ≥35 years**
Analysis	**Australasia**			
Main	0.26 (0.13, 0.49)	0.54 (0.29, 1.00)	0.21 (0.11, 0.41)	0.22 (0.11, 0.43)
Stable gen-pop HCV†	0.32 (0.17, 0.52)	0.66 (0.66, 1.06)	0.28 (0.28, 0.46)	0.30 (0.30, 0.49)
Decreasing HCV among PWID§	0.24 (0.11, 0.47)	0.54 (0.27, 1.09)	0.20 (0.09, 0.37)	0.20 (0.11, 0.40)
Halved PWID treatment rate, doubled for cirrhosis₡	0.12 (0.06, 0.24)	0.34 (0.18, 0.74)	0.21 (0.11, 0.44)	0.26 (0.15, 0.47)
Varied epidemic trajectories by region	0.43 (0.23, 0.85)	0.82 (0.46, 1.70)	0.37 (0.21, 0.73)	0.39 (0.21, 0.78)
25 additional treatments (rather than 50)	0.25 (0.15, 0.50)	0.52 (0.31, 1.04)	0.21 (0.11, 0.43)	0.21 (0.11, 0.45)
Analysis	**East & Southeast Asia**			
Main	0.26 (0.09, 0.49)	1.26 (0.70, 2.08)	0.19 (0.04, 0.39)	0.21 (0.04, 0.44)
Stable gen-pop HCV†	0.44 (0.25, 0.66)	1.43 (0.93, 2.22)	0.32 (0.16, 0.54)	0.37 (0.18, 0.59)
Decreasing HCV among PWID§	0.25 (0.09, 0.51)	1.27 (0.78, 2.19)	0.19 (0.04, 0.40)	0.21 (0.06, 0.44)
Halved PWID treatment rate, doubled for cirrhosis₡	0.13 (0.02, 0.30)	0.98 (0.54, 1.88)	0.19 (0.02, 0.47)	0.21 (0.05, 0.44)
Varied epidemic trajectories by region	0.40 (0.21, 0.62)	1.39 (0.87, 2.36)	0.31 (0.14, 0.48)	0.36 (0.16, 0.54)
25 additional treatments (rather than 50)	0.26 (0.08, 0.48)	1.23 (0.65, 1.99)	0.18 (0.04, 0.39)	0.22 (0.04, 0.44)
Analysis	**South Asia**			
Main	0.49 (0.25, 0.76)	1.86 (0.96, 2.75)	0.41 (0.21, 0.63)	0.43 (0.21, 0.67)
Stable gen-pop HCV†	0.78 (0.57, 0.96)	2.23 (1.23, 3.07)	0.64 (0.47, 0.80)	0.67 (0.49, 0.84)
Decreasing HCV among PWID§	0.47 (0.25, 0.75)	1.84 (0.97, 2.81)	0.38 (0.20, 0.62)	0.42 (0.22, 0.66)
Halved PWID treatment rate, doubled for cirrhosis₡	0.34 (0.15, 0.55)	1.33 (0.49, 2.17)	0.50 (0.26, 0.82)	0.41 (0.22, 0.66)
Varied epidemic trajectories by region	0.87 (0.66, 1.10)	2.35 (1.32, 3.35)	0.72 (0.52, 0.91)	0.75 (0.59, 0.95)
25 additional treatments (rather than 50)	0.48 (0.26, 0.74)	1.87 (0.98, 2.80)	0.40 (0.20, 0.62)	0.43 (0.21, 0.66)
Analysis	**North America**			
Main	0.58 (0.22, 1.13)	1.04 (0.44, 2.00)	0.46 (0.18, 0.90)	0.50 (0.20, 0.99)
Stable gen-pop HCV†	0.68 (0.33, 1.19)	1.13 (0.59, 2.14)	0.56 (0.29, 0.96)	0.60 (0.31, 1.05)
Decreasing HCV among PWID§	0.43 (0.16, 1.02)	0.81 (0.32, 1.77)	0.37 (0.13, 0.81)	0.39 (0.15, 0.89)
Halved PWID treatment rate, doubled for cirrhosis₡	0.23 (0.04, 0.48)	0.58 (0.25, 1.30)	0.42 (0.07, 0.92)	0.55 (0.14, 1.22)
Varied epidemic trajectories by region	0.60 (0.26, 1.08)	1.00 (0.51, 1.80)	0.50 (0.22, 0.88)	0.54 (0.24, 0.98)
25 additional treatments (rather than 50)	0.62 (0.18, 1.16)	1.07 (0.42, 1.98)	0.46 (0.15, 0.93)	0.54 (0.15, 1.04)

	Hepatitis C virus infections averted per treatment for infected individuals			
	Random allocation	**PWID**	**Cirrhotic**	**Age ≥35 years**
Analysis	**Western Europe**			
Main	0.32 (0.13, 0.68)	0.91 (0.51, 1.62)	0.24 (0.09, 0.53)	0.27 (0.10, 0.58)
Stable gen-pop HCV†	0.44 (0.21, 0.75)	1.02 (0.58, 1.61)	0.35 (0.15, 0.59)	0.38 (0.16, 0.65)
Decreasing HCV among PWID§	0.30 (0.10, 0.68)	0.94 (0.41, 1.55)	0.23 (0.08, 0.52)	0.25 (0.08, 0.58)
Halved PWID treatment rate, doubled for cirrhosis₡	0.10 (0.03, 0.24)	0.53 (0.26, 1.04)	0.20 (0.05, 0.43)	0.22 (0.07, 0.49)
Varied epidemic trajectories by region	0.45 (0.20, 0.88)	1.07 (0.60, 1.81)	0.37 (0.14, 0.70)	0.40 (0.17, 0.77)
25 additional treatments (rather than 50)	0.33 (0.13, 0.68)	0.94 (0.55, 1.58)	0.27 (0.11, 0.55)	0.28 (0.11, 0.58)
Analysis	**Sub-Saharan Africa**			
Main	0.75 (0.45, 1.10)	2.30 (1.38, 3.38)	0.60 (0.33, 0.89)	0.57 (0.33, 0.86)
Stable gen-pop HCV†	1.08 (0.79, 1.34)	2.69 (1.81, 3.83)	0.86 (0.61, 1.09)	0.85 (0.60, 1.06)
Decreasing HCV among PWID§	0.77 (0.48, 1.13)	2.24 (1.38, 3.37)	0.62 (0.38, 0.92)	0.58 (0.35, 0.86)
No later injecting start year for EE and SSA¶	0.72 (0.42, 1.06)	2.16 (1.41, 3.22)	0.57 (0.31, 0.85)	0.55 (0.33, 0.86)
Halved PWID treatment rate, doubled for cirrhosis₡	0.22 (0.02, 0.46)	0.16 (-0.10, 0.44)	0.38 (0.02, 0.74)	0.44 (0.02, 0.72)
Varied epidemic trajectories by region	0.80 (0.22, 1.20)	1.06 (0.06, 1.54)	0.66 (0.18, 1.00)	0.72 (0.20, 1.10)
25 additional treatments (rather than 50)	0.72 (0.20, 1.28)	1.04 (0.16, 1.60)	0.60 (0.16, 1.08)	0.64 (0.16, 1.16)
Analysis	**Latin America**			
Main	0.19 (0.03, 0.40)	0.18 (-0.01, 0.40)	0.15 (0.02, 0.32)	0.17 (0.02, 0.37)
Stable gen-pop HCV†	0.36 (0.15, 0.53)	0.24 (0.03, 0.46)	0.29 (0.11, 0.44)	0.32 (0.14, 0.49)
Decreasing HCV among PWID§	0.19 (0.03, 0.39)	0.24 (0.03, 0.50)	0.14 (0.02, 0.32)	0.16 (0.03, 0.36)
Halved PWID treatment rate, doubled for cirrhosis₡	0.08 (0.01, 0.23)	-0.08 (-0.23, 0.20)	0.14 (0.01, 0.37)	0.13 (0.01, 0.34)
Varied epidemic trajectories by region	0.25 (0.08, 0.44)	0.21 (0.01, 0.44)	0.20 (0.05, 0.37)	0.23 (0.07, 0.41)
25 additional treatments (rather than 50)	0.19 (0.03, 0.40)	0.16 (-0.02, 0.43)	0.15 (0.02, 0.32)	0.15 (0.02, 0.35)
Analysis	**Middle East & North Africa**			
Main	0.20 (0.09, 0.41)	0.84 (0.50, 1.39)	0.18 (0.08, 0.35)	0.19 (0.08, 0.36)
Stable gen-pop HCV†	0.33 (0.22, 0.58)	1.03 (0.63, 1.73)	0.30 (0.18, 0.51)	0.30 (0.19, 0.53)
Decreasing HCV among PWID§	0.20 (0.09, 0.40)	0.82 (0.52, 1.40)	0.17 (0.08, 0.35)	0.17 (0.08, 0.37)
Halved PWID treatment rate, doubled for cirrhosis₡	0.14 (0.06, 0.32)	0.65 (0.43, 1.20)	0.23 (0.11, 0.51)	0.19 (0.08, 0.39)
Varied epidemic trajectories by region	0.22 (0.13, 0.43)	0.85 (0.57, 1.41)	0.19 (0.12, 0.37)	0.19 (0.12, 0.38)
25 additional treatments (rather than 50)	0.18 (0.09, 0.39)	0.83 (0.52, 1.39)	0.17 (0.08, 0.33)	0.17 (0.08, 0.34)

EE: Eastern Europe; SSA: Sub-Saharan Africa

† Seeded at 101% of the general population HCV prevalence estimate

§ Seeded at the same number as the general population HCV prevalence estimate

¶ Eastern Europe and Sub-Saharan Africa seeded at 101% of the estimate of the proportion of adults that are PWID – the same as the other regions.

₡ The same number of treatments are given as in the main analyses but the treatment rate for PWID is halved, whilst the treatment rate for people with cirrhosis is doubled. The treatment rate for those who are neither PWID nor have cirrhosis is also altered and is either increased or decreased depending on the epidemic.

* Sensitivity analyses were run for 100 complete model runs to save computational time, as the results for 100 and 1,000 runs were similar.

Table 8.4: Sensitivity analysis where the proportion of adults that are PWID in the USA expands from 2010 onwards* - infections averted per treatment 2018-2038.

Original assumptions for the USA; point estimate (95% Credibility Intervals)			
Random allocation	**PWID**	**Cirrhotic**	**Age ≥35 years**
0.60 (0.24, 1.16)	1.08 (0.50, 2.06)	0.48 (0.20, 0.92)	0.52 (0.22, 1.02)
Assuming expanding PWID numbers after 2010 for the USA; point estimate (95% Credibility Intervals)			
Random allocation	**PWID**	**Cirrhotic**	**Age ≥35 years**
1.02 (0.30, 2.26)	1.92 (0.64, 3.92)	0.78 (0.24, 1.74)	0.84 (0.26, 1.84)

* From 2010 onwards the rate of initiating injecting is multiplied by 2.9 due to evidence of incidence of viral hepatitis C increasing by this amount between 2010 and 2015(57), which is thought to be driven by an increase in injecting drug use(330).

Table 8.5: HCV infections averted per treatment given in 2018 using the actual treatment numbers for 2017, compared with the estimates from the main model run treating 50 extra randomly allocated patients in 2018.

	HCV infections averted per treatment using actual 2017 treatment numbers for 2018			**Main model random allocation estimate (95% CrI)**
Country	**Infections averted (95% CrI)**	**Treatments**	**Infections averted per treatment (95% CrI)**	
Kazakhstan	462 (310, 749)	1750	0.26 (0.18, 0.43)	0.26 (0.18, 0.40)
Kyrgyzstan	42 (25, 68)	100	0.42 (0.25, 0.68)	0.42 (0.24, 0.62)
Tajikistan	NA	0	NA	0.50 (0.24, 0.76)
Turkmenistan	NA	0	NA	0.40 (0.20, 0.64)
Uzbekistan	490 (205, 880)	1500	0.33 (0.14, 0.59)	0.30 (0.10, 0.56)
Armenia	NA	0	NA	0.12 (0.02, 0.26)
Azerbaijan	50 (18, 97)	210	0.24 (0.09, 0.46)	0.24 (0.06, 0.46)
Belarus	NA	0	NA	0.00 (-0.10, 0.14)
Bosnia	NA	0	NA	0.00 (-0.12, 0.14)
Bulgaria	4 (-12, 46)	350	0.01 (-0.03, 0.13)	0.02 (-0.04, 0.10)
Czechia	697 (456, 1338)	910	0.77 (0.50, 1.47)	0.80 (0.54, 1.46)
Estonia	286 (40, 634)	908	0.31 (0.04, 0.70)	0.40 (0.08, 0.80)
Georgia	6432 (2720, 10195)	15400	0.42 (0.18, 0.66)	0.40 (0.14, 0.72)
Hungary	313 (76, 670)	1477	0.21 (0.05, 0.45)	0.20 (0.06, 0.42)
Latvia	45 (-75, 246)	1071	0.04 (-0.07, 0.23)	0.06 (-0.06, 0.26)
Lithuania	278 (109, 547)	1518	0.18 (0.07, 0.36)	0.18 (0.08, 0.36)
Moldova	38 (3, 96)	300	0.13 (0.01, 0.32)	0.14 (0.02, 0.30)
Poland	617 (32, 1348)	5800	0.11 (0.01, 0.23)	0.10 (0.00, 0.26)
Romania	-220 (-627, 675)	8131	-0.03 (-0.08, 0.08)	-0.02 (-0.08, 0.06)
Russia	105 (-364, 669)	5500	0.02 (-0.07, 0.12)	0.02 (-0.06, 0.14)
Slovakia	27 (-10, 100)	316	0.09 (-0.03, 0.32)	0.08 (-0.06, 0.28)
Ukraine	188 (87, 387)	1750	0.11 (0.05, 0.22)	0.10 (0.06, 0.22)
Australia	7212 (4814, 12638)	30000	0.24 (0.16, 0.42)	0.24 (0.14, 0.40)

Country	HCV infections averted per treatment using actual 2017 treatment numbers for 2018			Main model random allocation estimate (95% CrI)
	Infections averted (95% CrI)	Treatments	Infections averted per treatment (95% CrI)	
New Zealand	600 (86, 1348)	1882	0.32 (0.05, 0.72)	0.34 (0.06, 0.90)
China	25550 (12009, 45947)	100000	0.26 (0.12, 0.46)	0.24 (0.10, 0.44)
Indonesia	59 (-31, 218)	600	0.10 (-0.05, 0.36)	0.12 (-0.04, 0.36)
Japan	15487 (6298, 36518)	38000	0.41 (0.17, 0.96)	0.46 (0.18, 0.88)
Malaysia	167 (68, 352)	550	0.30 (0.12, 0.64)	0.32 (0.10, 0.56)
Myanmar	636 (357, 1078)	2000	0.32 (0.18, 0.54)	0.30 (0.18, 0.50)
Philippines	216 (86, 382)	550	0.39 (0.16, 0.69)	0.38 (0.16, 0.64)
Taiwan	293 (-44, 1053)	4000	0.07 (-0.01, 0.26)	0.06 (-0.02, 0.26)
Thailand	514 (-21, 1000)	3000	0.17 (-0.01, 0.33)	0.16 (0.00, 0.38)
Viet Nam	1084 (220, 2286)	4500	0.24 (0.05, 0.51)	0.24 (0.06, 0.44)
Afghanistan	8 (3, 13)	10	0.80 (0.30, 1.30)	0.86 (0.34, 1.34)
Bangladesh	NA	0	NA	0.40 (0.20, 0.66)
India	50483 (27622, 77496)	115000	0.44 (0.24, 0.67)	0.44 (0.22, 0.70)
Iran	1876 (724, 3918)	6000	0.31 (0.12, 0.65)	0.32 (0.10, 0.64)
Nepal	NA	0	NA	0.30 (0.08, 0.56)
Pakistan	86866 (46250, 139750)	161000	0.54 (0.29, 0.87)	0.58 (0.32, 0.86)
Canada	2778 (-388, 7292)	9500	0.29 (-0.04, 0.77)	0.30 (-0.06, 0.72)
USA	156699 (66000, 281011)	231000	0.68 (0.29, 1.22)	0.60 (0.24, 1.16)
Albania	5 (1, 11)	48	0.10 (0.02, 0.23)	0.10 (0.04, 0.24)
Austria	982 (582, 1748)	1500	0.65 (0.39, 1.17)	0.66 (0.38, 1.08)
Belgium	295 (68, 684)	1080	0.27 (0.06, 0.63)	0.26 (0.06, 0.70)
Croatia	24 (10, 46)	150	0.16 (0.07, 0.31)	0.16 (0.06, 0.32)
Cyprus	13 (4, 25)	46	0.28 (0.09, 0.54)	0.32 (0.10, 0.56)
Denmark	187 (138, 251)	511	0.37 (0.27, 0.49)	0.38 (0.28, 0.52)
Finland	17 (-4, 50)	300	0.06 (-0.01, 0.17)	0.06 (-0.02, 0.16)
France	5460 (3162, 11258)	19300	0.28 (0.16, 0.58)	0.28 (0.14, 0.60)
Germany	4823 (2042, 10455)	13000	0.37 (0.16, 0.80)	0.40 (0.18, 0.80)
Greece	239 (74, 440)	1134	0.21 (0.07, 0.39)	0.22 (0.04, 0.42)
Iceland	59 (40, 77)	200	0.30 (0.20, 0.39)	0.26 (0.18, 0.38)
Ireland	163 (36, 392)	840	0.19 (0.04, 0.47)	0.22 (0.06, 0.44)
Italy	9669 (3535, 21828)	43000	0.22 (0.08, 0.51)	0.24 (0.08, 0.50)
Luxembourg	259 (50, 441)	300	0.86 (0.17, 1.47)	0.94 (0.28, 1.60)
Macedonia	6 (3, 19)	76	0.08 (0.04, 0.25)	0.08 (0.04, 0.22)
Malta	25 (15, 43)	70	0.36 (0.21, 0.61)	0.36 (0.20, 0.64)
Montenegro	NA	0	NA	0.12 (0.08, 0.22)
Netherlands	336 (157, 660)	1200	0.28 (0.13, 0.55)	0.28 (0.12, 0.58)
Norway	622 (368, 980)	1000	0.62 (0.37, 0.98)	0.64 (0.40, 0.94)
Portugal	1149 (295, 2136)	4836	0.24 (0.06, 0.44)	0.24 (0.06, 0.46)
Serbia	NA	0	NA	0.30 (0.22, 0.38)
Slovenia	102 (74, 143)	200	0.51 (0.37, 0.72)	0.52 (0.38, 0.74)
Spain	6099 (1988, 12549)	29700	0.21 (0.07, 0.42)	0.20 (0.08, 0.50)
Sweden	1459 (452, 2518)	2500	0.58 (0.18, 1.01)	0.62 (0.10, 1.18)

Country	HCV infections averted per treatment using actual 2017 treatment numbers for 2018			Main model random allocation estimate (95% CrI)
	Infections averted (95% CrI)	Treatments	Infections averted per treatment (95% CrI)	
Switzerland	1149 (572, 2138)	3200	0.36 (0.18, 0.67)	0.38 (0.18, 0.64)
UK	7241 (3046, 15826)	14800	0.49 (0.21, 1.07)	0.50 (0.22, 1.22)
Ghana	13 (8, 19)	20	0.65 (0.40, 0.95)	0.66 (0.40, 0.98)
Kenya	4 (2, 6)	6	0.67 (0.33, 1.00)	0.68 (0.38, 1.04)
Madagascar	2 (1, 3)	3	0.67 (0.33, 1.00)	0.76 (0.44, 1.16)
Mauritius	NA	0	NA	-0.10 (-0.26, 0.10)
Mozambique	NA	0	NA	0.62 (0.28, 0.96)
Nigeria	240 (156, 330)	300	0.80 (0.52, 1.10)	0.76 (0.46, 1.12)
Senegal	NA	0	NA	0.76 (0.46, 1.14)
Tanzania	NA	0	NA	0.84 (0.54, 1.18)
Argentina	275 (77, 514)	1204	0.23 (0.06, 0.43)	0.24 (0.06, 0.46)
Brazil	8834 (3135, 17196)	45016	0.20 (0.07, 0.38)	0.22 (0.08, 0.40)
Mexico	58 (-35, 174)	480	0.12 (-0.07, 0.36)	0.12 (-0.08, 0.36)
Uruguay	NA	0	NA	0.28 (0.12, 0.46)
Egypt	111166 (54718, 238400)	600000	0.19 (0.09, 0.40)	0.18 (0.08, 0.38)
Israel	913 (572, 1282)	1500	0.61 (0.38, 0.85)	0.62 (0.38, 0.88)
Lebanon	299 (182, 484)	325	0.92 (0.56, 1.49)	0.92 (0.58, 1.44)
Libya	64 (0, 133)	288	0.22 (0.00, 0.46)	0.20 (0.00, 0.42)
Morocco	2479 (1302, 4376)	8000	0.31 (0.16, 0.55)	0.34 (0.16, 0.54)
Saudi Arabia	329 (-57, 1192)	2800	0.12 (-0.02, 0.43)	0.08 (-0.02, 0.40)
Syria	4 (2, 7)	10	0.40 (0.20, 0.70)	0.38 (0.18, 0.66)
Tunisia	279 (108, 570)	1000	0.28 (0.11, 0.57)	0.26 (0.12, 0.50)
Turkey	40 (23, 74)	194	0.21 (0.12, 0.38)	0.22 (0.12, 0.42)
Total	525764 (243948, 980523)	1554720		0.34 (0.16, 0.63)

8.4. Discussion

8.4.1. Main findings

My modelling suggests that one infection will be prevented over the next 20 years for every three randomly allocated HCV treatments undertaken globally. The number of HCV infections that are averted will vary by region and country, with twenty randomly allocated treatments being needed to prevent one infection in Eastern Europe, but less than two in Sub-Saharan Africa. Targeting treatment to people aged ≥35 or with cirrhosis is likely to produce similar prevention benefits. However, targeting PWID could achieve greater impact, with over one infection being prevented for every PWID treated globally but with impact varying considerably by country and region. Results suggest the prevention impact of randomly allocating treatment or treating PWID will be greater in countries with high population growth and higher percentage of adults that are PWID but will be reduced in countries with high HCV prevalence among PWID and the general population, due to greater re-infection following treatment. The number of treatments given in 2017 was not associated with the number of infections averted per treatment. In sensitivity analyses, assuming a stable general population HCV prevalence, rather than decreasing, or varying HCV epidemic trajectories by region resulted in more infections averted per treatment. Whereas, assuming that treatment rates among PWID are halved and doubled for those with cirrhosis resulted in fewer infections averted per treatment, as targeting PWID will result in higher potential prevention benefits.

8.4.2. Strengths and limitations

Section 7.4.3 discusses the strengths and limitations of the model used and the data that parameterise it. The analysis in this chapter, commissioned by the WHO to focus on the prevention benefits of a treat-all policy, does not consider morbidity or mortality benefits. These outcomes have been considered in previous economic models, which emphasise the importance of treating individuals with cirrhosis for reducing the burden of liver-related deaths(79, 240). This model does not consider the impact of scaling up prevention interventions (eg. opiate substitution treatment [OST] and needle and syringe programs [NSP]) as the WHO's focus was the prevention benefits of treatment. Countries are at varying stages of treatment scale-up(409), therefore the extra 50 treatments given may

impact differently across settings. To investigate this, I included the number of treatments in 2017 in the regression analyses, which found no effect of baseline treatment numbers. I also examined this issue in a sensitivity analysis which considered the impact of additional treatment rates, suggesting similar infections averted per treatment.

8.4.3. Comparison to other studies

Other modelling analyses have considered the prevention benefits of HCV treatment among PWID, MSM, and the general population(28, 34, 70, 86, 144, 218, 234, 235, 239, 240), with Martin et al. finding higher infections averted per treatment when treating PWID than ex/non-PWID with lower infection rates(240). Similarly to this chapter, some analyses of PWID HCV epidemics have also suggested that less prevention benefit will be achieved in settings with higher or increasing HCV prevalence among PWID(73, 110, 235, 240). The global HCV modelling analysis by Heffernan et al. that also identified negative infections averted when the pool of susceptible individuals is increased in certain settings where HCV prevalence among PWID was very high, although they did not estimate infections averted per treatment(150). Ayoub et al.'s modelling study in Egypt found between 0.08 and 0.11 infections averted per treatment over 15 years, similar to the 0.18 (95% CrI: 0.08, 0.38) that I found for the treat-all strategy(28). Meanwhile, a modelling paper by Lim et al. in Pakistan found 0.56 infections averted in Pakistan over 15 years, whilst in Pakistan I found 0.58 (95% CrI: 0.32, 0.86) infections averted over 20 years(218).

8.4.4. Implications

These analyses show that globally, a moderate prevention impact (one infection prevented per three treatments undertaken) can be achieved with a treat-all strategy, with greatest benefit achieved in countries with high population growth, including many LMICs and countries such as Pakistan and India that were investigated in chapters 4 and 5. These findings are useful for policy-makers as they provide an understanding of the prevention benefits of widespread treatment scale-up when planning for the WHO 2030 HCV elimination targets(402). The analyses suggest that countries in some regions, such as Sub-Saharan Africa and South Asia, could achieve greater prevention benefits from scaling up

treatment than other regions, such as Eastern Europe and Latin America, due to having growing populations and generalised epidemics. However, many countries lack the resources to treat HCV(125), or screening may present a barrier to treatment scale-up due to their HCV epidemics being generalised(76). This issue will be particularly pertinent for countries with high burdens of other infectious diseases, where policy makers may focus their resources on more acute diseases rather than HCV. Only with substantial donor support, or considerable improvements in access to HCV DAA therapies and diagnostic tests, will such countries be able to substantially scale-up treatment for HCV.

Importantly, my analyses also re-emphasized the prevention benefits of targeting PWID, as PWID were the subgroup for whom treatment produced the most infections averted globally and for most countries. This is due to the higher likelihood of PWID transmitting HCV relative to other subgroups(169). In chapter 7, I found that HCV transmission risks associated with IDU will account for 43% of all transmission globally from 2018 to 2030, so it is key that PWID are allowed access to treatment. However, PWID comprise only a fraction of the overall HCV burden globally(127), and so any elimination strategy must also target other groups, especially in settings with high rates of infection due to nosocomial factors, such as Pakistan (chapter 4)(218, 371). In the DAA era of treatment as prevention, reinfection rates are now being estimated and have been high in some settings, for example 21.5 re-infections per 100 person-years in Dundee(322), and low in others, such as 3.1 per 100 person-years in British Columbia, although this rate was 10.2 per 100 person-years among younger PWID(315). In scenarios where infection rates are high, treatment rates among PWID need to be increased to high levels and HCV prevention interventions (OST and NSP) need to be scaled up to reduce these high re-infection risks(150, 287). Either way, these insights emphasise the need to allocate resources to treating PWID, either due to the greater prevention benefits achieved and/or to gain control of the epidemic among PWID; crucial for achieving elimination.

8.4.5. Conclusions

In this chapter, I used dynamic HCV transmission modelling to determine the HCV infections averted per DAA treatment at a global, regional, and country-level for a random treat-all strategy, comparing it to treating other subgroups (PWID, people with cirrhosis,

and people aged over 35), and evaluating how the impact achieved depends on different country-specific factors. This chapter's findings highlight that, globally, treating PWID averts the most infections per treatment. A treat-all strategy, treating those aged ≥35 years, or those with cirrhosis all avert roughly the same amount of infections. However, impact will vary by region and country, with negative infections being averted for PWID in some countries with very high HCV prevalence rates among PWID and some countries getting more impact from treating randomly rather than targeting PWID. The WHO's 2030 HCV elimination targets(403) include aims for reducing both HCV-related mortality and HCV incidence. Other analyses have shown that treating those with advanced liver disease is the best strategy for reducing HCV-related mortality(79, 240). The results in the chapter 7 indicated that reducing HCV incidence in PWID will be necessary for reaching the global HCV incidence target. The results of previous analyses have shown that targeting treatment at PWID is one method that can help achieve such as reduction, via treatment as prevention(70, 109), with this chapter suggesting that that many HCV infections would be averted through this strategy. The work in this chapter was commissioned as part of the WHO's new guidelines for a treat-all strategy(408). Such a strategy would reduce practical obstacles to treatment, such as screening to prioritise individuals with advanced disease, and could be considered more equitable by allowing all those who seek treatment to access it, including often stigmatised groups such as PWID(77). There are other issues to consider, mainly surrounding resourcing for the costs of testing and treatment and ensuring that those with severe liver disease are treated. However, on a global scale, a treat-all strategy as outlined by the WHO is advisable as it allows flexibility regarding the epidemiology of HCV in different settings.

CHAPTER 9. DISCUSSION

In this thesis, I investigated the epidemiology of HCV in different settings around the world. Firstly, I used data from two household serosurveys to look at the associations between various risk factors and HCV prevalence in two generalised epidemics settings: Pakistan and Punjab, India. Secondly, I developed a global model of country-level HCV epidemics to estimate the contribution of injecting drug use (IDU) to global HCV transmission and to quantify the prevention benefits of HCV treatment when targeted to different subgroups of infected individuals. This second analysis focussed on the benefits of a treat-all strategy, as outlined in the WHO's 2018 HCV guidelines, and compared that to what is achieved through targeting other subgroups. In this discussion chapter, I will recap the main findings and their implications, discuss the limitations of each chapter, and consider how this work could be developed further.

In chapter 4, I focused on Pakistan using a national serosurvey with an estimated anti-HCV prevalence of around 4.8%(371). I found that healthcare-related exposures, including childbirth and the number of medical injections received in the last year, were associated with prevalent HCV infection(371). I also found that low socio-economic status, marriage, and some common community risk exposures, such as going to a barber, were associated with an increased risk of HCV infection. These findings add weight to the evidence that unsafe healthcare interventions are important contributors to Pakistan's HCV epidemic(10), but also suggest that a range of other exposures could be contributing to the epidemic. Several of these associations are likely markers for other risk factors. For example, low socio-economic status could result in poor access to quality healthcare(177), whilst marriage may be acting as a marker of either intrafamilial transmission or shared risk factors outside of the household, which requires further investigation(280). A limitation of the serosurvey in Pakistan is that it did not ask about transmission routes such as male circumcision(281), female genital mutilation(187), or childbirth, which had to be estimated indirectly. The findings of this serosurvey may not be generalisable to other settings, even those with high HCV prevalences. For instance, some risk factors identified may be particularly prevalent in Pakistan, whilst some medical exposures may not carry the same risk in other locations.

In chapter 5, I found an anti-HCV prevalence of 3.6% in a serosurvey of Punjab state, India(346). Living in rural areas, being aged 40-59, and being male were all positively associated with HCV infection, which was more common among those that had received a

blood transfusion, or had low levels of education, and not receiving their last medical injection from a medical doctor(346). These associations suggest that several health-related exposures are important in Punjab, India, whilst the associations with low education and rural areas likely indicate that other HCV transmitting behaviours or practices are common among these subgroups. Similarly to the serosurvey in Pakistan, the findings from Punjab are not necessarily generalisable to other HCV epidemic settings. Likewise, this serosurvey did not include questions about all possible risk factors, such as male circumcision(16). Only five respondents, 0.1% of those sampled, reported that they had ever injected drugs. This could be an accurate estimate, with small numbers being reported due to the relatively modest overall sample size (n=5,543) or could be under-reported due to issues of social-desirability bias, a problem common to all household serosurveys and one that may also affect other variables, as is the case with recall bias. Additionally, it could be that many people who inject drugs (PWID) are homeless or incarcerated and so would not be picked up by a household survey resulting in an under-estimate. The sampling frame used in the Punjab serosurvey excluded newly built peri-urbans slums, which could also lead to an under ascertainment of IDU due to poverty being common among PWID(368).

A universal weakness of this type of cross-sectional serosurvey, including the Pakistan and Punjab serosurveys, is that it is impossible to ascertain when the infections occurred. This means that whilst many of the questions are asking about behaviours in the last year or six months, the individuals may have been infected many years ago, before the scope of the question, which may mean that the importance of some risk factors is underestimated. An example of this, for both Pakistan and Punjab, is the relatively weak association between medical injections and HCV, which is known to be a key risk factor for HCV in both settings(10, 80). Unfortunately, the current contribution of unsafe medical injections is unclear as a huge reduction in the number of new HCV infections due to unsafe medical injections has been estimated between 2000 and 2010(283). This limitation of timeliness does not mean the results are without implications. Determining associations with prevalent infections is still of use for understanding a setting's HCV epidemiology and for designing screening programmes where knowing who is likely to be infected allows for targeting of testing to subgroups with specific risk behaviours that are likely to have a higher yield of infected individuals. Other analyses have highlighted the advantages of designing screening algorithms that account for the results of serosurveys, with a study of 87,000 people attending an outpatient clinic in Pakistan using such a system, identifying 5,000 people to be

tested, which had a 38% anti-HCV prevalence(191). This understanding of a setting's epidemiology becomes particularly important later in the course of testing and treatment programmes when the number of infected individuals is lower and risk-based screening strategies become more useful.

Whilst chapters 4 and 5 looked at risk factors for HCV infection in two generalised epidemics, chapter 7 used modelling to look at the concentration of epidemics by attempting to quantify the contribution of IDU to global HCV epidemics. I estimated that globally, around 43% of all HCV transmission between 2018 and 2030 will be due to IDU, varying from 14% in Sub-Saharan Africa to 96% in Eastern Europe(373). This quantification of the importance of IDU to future HCV transmission is important for country-level policy makers, allowing them to better understand the degree to which they should allocate resources to PWID. Whilst in some countries the contribution of IDU is low, for example 6% in India and 18% in Pakistan, these findings show that globally it will not be possible to hit the WHO's 2030 targets for an 80% reduction in incidence without hugely reducing transmission among PWID(403). This is particularly important in high-income countries where the contribution of IDU is 79%. This reduction in transmission among PWID could be brought about through various evidence-based methods such as needle and syringe provision (NSP), opiate substitution therapy (OST)(288), or through using HCV treatment as a prevention strategy(109), which I went on to investigate in chapter 8.

Whereas in chapters 4, 5, and 7 I investigated risk factors for prevalent and incident infections, chapter 8 looked at averting infections through treatment as prevention for different infected subgroups. I found that globally, on average, treating PWID resulted in more infections averted per treatment, 1.27 over twenty years, than other infected subgroups due to high transmission rates. I also found that a treat-all strategy, as outlined in the WHO's 2018 HCV guidelines(408), for which these analyses were commissioned(410), would on average avert 0.35 infections per treatment over twenty years. Treating infected individuals aged over 30 years or those with cirrhosis would avert a similar, but slightly lower amount of infections to a treat-all strategy.

The number of infections averted with a treat-all strategy varied by region, from 0.06 per treatment over twenty years in Eastern Europe to 0.75 in Sub-Saharan Africa. When treating infected PWID the regional number of infections averted varied from 0.14 per treatment over twenty years in Eastern Europe to 2.30 in Sub-Saharan Africa, whilst at country-level

4.82 infections were averted per treatment in Madagascar and -0.52 in Mauritius (with negative infections averted indicating reinfection of those treated). The number of infections averted with a treat-all strategy was positively associated with higher population growth and the percentage of adults that are PWID, and negatively associated with the HCV prevalence among PWID and the general population, whilst the number averted by treating PWID was associated with the same factors. This study quantifies treatment as prevention on a global scale and highlights how the epidemiology in a setting affects how many infections are averted. These findings support, and are quoted as such, for the WHO's recommendations for a treat-all strategy, irrespective of disease stage(408, 410).

The findings of chapter 8 can help those designing treatment programmes in settings such as Pakistan(255) and Punjab, India(80), to understand how treating specific subgroups will affect the number of treatments that will be required to meet the WHO's elimination targets(403). However, the model only produced results at country-level, so would have to be adapted for a particular sub-national setting such as Punjab, which does not have the same epidemic characteristics as India overall(121), with Punjab having a much higher HCV prevalence than India(121).

Additionally, a limitation of the modelling in chapter 8 is that it does not examine the effect that varying stages of treatment scale-up would have on the number of infections averted for each country. Modelling work by Metzig et al. focused on PWID, found that the increased pool of susceptibles becoming reinfected at very low levels of treatment coverage reduces the effect of treatment as prevention(251). However, as coverage subsequently increases to a level that is sufficiently large then treatment as prevention becomes more effective(251). Using 50 treatments for HCV to investigate the number of infections averted across different countries can be difficult to interpret as whilst 50 is a very small number of additional treatments for a setting such as Pakistan, it is a large amount for a country such as Iceland. The role of scale-up on treatment as prevention across these diverse settings included in this chapter of my thesis could be investigated in detail in future modelling.

Suitable data to allow me to build the models used in chapters 7 and 8 were only available for 88 countries, which, although constituting 85% of the world's population, is less than half of all the countries in the world. This highlights the paucity of epidemiological data regarding the number of PWID in many countries, as well as a lack of data on HCV prevalences among PWID and the general population. Additionally, where data were

available for a country, one or more of these important parameters for building the model were often graded as low-quality by the literature review it was taken from. Of the 88 countries included, only 19 had all three key parameters rated as moderate or better. This lack of good quality data highlights there is a large gap in the evidence. Future modelling exercises such as those presented here would benefit from better quality data from more countries, particularly in Sub-Saharan Africa.

Other data that could improve the models were also lacking. Data on migration were not available for all countries included in the models, particularly in low- and middle-income countries. There was also a lack of information on the prevalence of HCV among migrants, which is likely to be lower than the prevalence of HCV of their source country because of a healthy migrant effect where only those in good health or those that are wealthier are able to migrate(120). Whilst one review has looked at this for migration from endemic regions to high-income countries(128), and studies have investigated the contribution of migration to HCV in the EU(99, 302), data is not available for many of the countries that we modelled. The models could be further improved if there were country-level, longitudinal data available that quantified the risks due to particular risk factors such as unsafe medical injections. Data detailing the availability of OST and NSP over time, including when they were first implemented in each country, were not available at the time of writing. Such data would allow an in-depth look at how such interventions affect the ongoing HCV epidemics in each country. Although other modelling analyses have managed to use current estimates of intervention coverage(209), indicating that the current data can be used if certain assumptions are made, these model projections had to make a number of simplifying assumptions.

My findings in chapter 4, on the contributions of various risks in the Pakistan serosurvey(371), have fed into a detailed mathematical modelling analysis of Pakistan's HCV epidemic(218). Further modelling using the results of my analyses on the serosurvey in Pakistan is underway, incorporating testing into the model. My results in chapter 5 from the serosurvey in Punjab, India(346), could be used to develop a detailed mathematical model of the HCV epidemic in that setting. This model could use the results of the serosurvey to model different screening strategies to estimate the number of individuals that require testing and treating for meeting the WHO's 2030 elimination targets(403). Such a model

could also ascertain whether Punjab's treatment programme is currently on track to meet these targets and, if not, what is needed to meet them(80).

My results in chapter 7 showed that IDU is a key contributor for HCV transmission in most settings around the world, so future modelling exercises should endeavour to take the role of IDU into account(373). As further data becomes available, the model used in chapters 7 and 8 could be applied to other countries, allowing for the estimation of the contribution of HCV due to IDU in that setting and quantifying the effect of treatment as prevention. The models could also be adapted to settings where more detailed information is available, which is the case for Indonesia where a project is underway looking at what is required for elimination and estimating the associated costs. Additionally, the models could be extended in a similar way globally, as in a recently published study detailing how elimination can be reached on a worldwide scale(150). Such an analysis could be improved upon by incorporating key data when it becomes available, such as on HCV among migrants and longitudinal trends in NSP and OST coverage. With better data on HCV and its risk factors, models can more fully describe an HCV epidemic in a particular setting and the likely effect of interventions.

To conclude, I hope that the findings of this thesis will be further used by policy makers designing HCV testing and treatment programmes in the hope of meeting the WHO's 2030 elimination targets(403). The work in this thesis is particularly relevant for those designing testing programmes in Pakistan(255) and Punjab, India(80), which contain a large segment (around 14%) of the global burden of HCV(40). However, the work is also relevant for those looking to understand how to best allocate resources to reduce the transmission of HCV in dozens of countries globally. For meeting the WHO's targets, my work highlights the importance of reducing transmission among PWID and that allowing access to DAA treatment for PWID could result in many infections averted globally(403). Overall, my work in this thesis adds to the body of evidence for understanding the epidemiology of HCV in various settings around the world, which will be vital if the WHO's 2030 HCV elimination targets are to be met.

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APPENDICES

APPENDIX TO CHAPTER 4

Appendix figure 4.1: Pakistan HCV serosurvey questionnaire, household.

Determination of Prevalence of Hepatitis B & C in General Population

HOUSEHOLD PROFORMA

1. **PSU No.** : [redacted] 2. **P.S.U. Name :** _____

3. **Province :** _____ صوبہ 4. **Mother tongue :** _____ مادری زبان

5. **Name of Respondent:** [redacted] _____

6. **Address :** [redacted] _____

7. **Type of material used in dwelling:** کس قسم کا مکان ہے ☐

1. Kacha کچا 2. Pacca پکا 3. Semi-pacca / kacha نیم پکا/ آدھا کچا 4.Well furnished شاندار بنگلہ (خوب سجا ہوا)

8. **Is the house:** آپ اس مکان میں کیسے رہتے ہیں؟ ☐

1. Own ذاتی ہے 2.Rented کرائے پر ہے 3.Rent Free کرائے کے بغیر ہے 4.Others دیگر

9. **Source of drinking water:.** پینے کے پانی کا ذریعہ ☐

1. Piped in dwelling مکان کے اندر نلکا ہے 2. Public Tap سرکاری نلکا 3. Spring/Pound/ River/ stream چشمہ / تالاب اور دریا ندی

4. Well کنواں 5. Tanker, vendor پانی کا ٹینکر، پانی لا کر بیچنے والا 6. Other (Specify) دیگر وضاحت کریں ☐

10. **Toilet facility:** رفع حاجت کی سہولت 1. Flush to sewage system فلش سسٹم 2. Pit--latrine. گڑھے والی لیٹرین

3. No facility/field کوئی سہولت نہیں / کھیت

11. **Did any member of this household died during last 02 years:** ☐

1= Yes, ہاں 2=No, نہیں 9=DK معلوم نہیں

S.# نمبر شمار	Name [redacted]	Relation with Head of Household سربراہ سے رشتہ	Sex جنس 1=M 2=F مرد / عورت	Age عمر سالوں میں	Cause of Death وفات کی وجہ	Place of death وفات کہاں ہوئی	Occupation of the deceased person مرنے والے کا پیشہ
1.							
2.							
3.							
4.							
5.							

Appendix figure 4.2: Pakistan HCV serosurvey questionnaire, individual.

Determination of Prevalence of Hepatitis B & C in General Population

PROFORMA FOR INDIVIDUALS

1. Person ID # [redacted] 2. P.S.U. Name:

3. Name: [redacted]

4. Age: (عمر(سالوں میں) 5. Gender (M/F): (مرد/عورت)

6. Marital Status: Single / Married / widow / widower / separated / divorced
ازدواجی حیثیت کنوارہ/کنواری شادی شدہ بیوہ رنڈوا علیحدہ طلاق شدہ

Key: 1=Yes, ہاں 2 =No نہیں 9=DK معلوم نہیں

7	Do you have jaundice ? کیا آپ کو آج کل یرقان ہے؟	☐	ہاں ☐ نہیں ☐ معلوم نہیں
	If yes, duration in months اگر ہاں تو کتنے مہینوں سے ہے؟		
8	Did you ever had jaundice? کیا آپ کو پہلے کبھی یرقان ہوا؟	☐	ہاں ☐ نہیں ☐ معلوم نہیں
	If yes, year of jaundice اگر ہاں تو کس سال ہوا تھا؟		
9	Did you know about hepatitis? کیا آپ ہیپاٹائٹس کے بارے میں جانتے ہیں؟	☐	ہاں ☐ نہیں
10	If yes through which source you became aware of hepatitis? اگر ہاں تو آپ کو ہیپاٹائٹس کے بارے میں آگاہی کیسے ہوئی؟		
	1۔ٹی وی سے ☐ 2۔اخبار سے ☐ 3۔ریڈیو سے ☐ 4۔انٹرنیٹ سے ☐ 5۔دوست/رشتے دار سے ☐ 6۔ڈاکٹر سے ☐ 7۔دیگر سے		
11	Is any family member suffering from hepatitis, B or C? کیا گھر کے کسی فرد کو ہیپاٹائٹس بی یا سی ہے؟	☐	ہاں ☐ نہیں ☐ معلوم نہیں
	If yes, who (relation) اگر ہاں تو کس کو (رشتہ)		
12	Did any family member die of liver disease? کیا گھر کا کوئی فرد جگر کی بیماری سے فوت ہوا؟	☐	ہاں ☐ نہیں ☐ معلوم نہیں
	If yes, who (relation) اگر ہاں تو کون (رشتہ)		
13	Do you shave? کیا آپ شیو کرتے ہیں؟	☐	ہاں ☐ نہیں
	If yes, where do you get your shave done 1.Home گھر 2.Barber حجام 3.Both دونوں اگر ہاں تو آپ کہاں سے شیو کرواتے ہیں؟		
14	Do you share hukkah/ cigarettes/ bidi? کیا آپ ایک دوسرے کا حقہ/سگریٹ یا بیڑی استعمال کرتے ہیں؟	☐	ہاں ☐ نہیں
15	Do you share tooth brush/miswak/razors etc? کیا آپ کسی کا استعمال شدہ ٹوتھ برش، مسواک یا اُسترہ استعمال کرتے ہیں؟	☐	ہاں ☐ نہیں
16	Have you had ear/nose piercing? کیا آپ نے کان یا ناک چھدوائے ہیں؟	☐	ہاں ☐ نہیں
	If yes: اگر ہاں تو کیا 1-with needle سوئی کے ساتھ 2-Device آلے کے ساتھ 9-Don't know معلوم نہیں		
17	Have you had tattooing/ acupuncture? کیا آپ نے ٹیٹو/گودنا یا نقش نگاری کروائی ہے؟	☐	ہاں ☐ نہیں
18	Do you perform matam with chain/knives? کیا آپ زنجیر یا چھریوں سے ماتم کرتے ہیں؟	☐	ہاں ☐ نہیں
	If yes: اگر ہاں تو کیا یہ 1- Own ذاتی ہیں 2- Share مشترکہ 9- DK معلوم نہیں		

19	Any history of surgery? کیا کبھی آپ کا اپریشن ہوا ہے؟ 1- Yes ہاں 2- No نہیں	Year سال	Blood Transfusion انتقال خون	No. of Units کتنے یونٹ
	Caesarean بڑا اپریشن (بچے کیلئے)			
	Gall bladder پتہ			
	Appendix اپینڈکس			
	Heart دل			
	Others دیگر			
	Fracture/accident ہڈی ٹوٹنا/حادثہ			
	Dental treatment دانتوں کا علاج (صفائی، بھرائی، نکلوانا)			

20	History of IV/IM injection جب بیمار ہوتے ہیں تو کیا گوشت یا نس میں ٹیکہ لگواتے ہیں		
	If yes: How often/year: 1. 2-5, 2. 5-10, 3. More than 10 اگر ہاں تو سال میں کتنی مرتبہ		
	Type of syringe used: 1= New disposable نئی ڈسپوزیبل 2= Re-used syringe شیشے یا پلاسٹک کی دوبارہ استعمال کی گئی سرنج 9. Don't know معلوم نہیں سرنج کیسی تھی؟		
21	History of haemodialysis (if yes: year) کیا کبھی ہیموڈائیلاسس کروایا ہے؟ اگر ہاں تو کس سال	☐	ہاں ☐ نہیں
22	History of hospitalization (if yes: year) کیا کبھی ہسپتال میں داخل ہوئے؟ اگر ہاں تو کس سال	☐	ہاں ☐ نہیں
23	History of use of intravenous drugs کیا آپ نس کے ذریعے نشہ کرتے ہیں؟	☐	ہاں ☐ نہیں
24	Have you had hepatitis "B" vaccination کیا آپ نے ہیپاٹائٹس B کے بچاؤ کے ٹیکے لگوائے ہیں؟	☐	ہاں ☐ نہیں

-: 3 :-

APPENDIX TO CHAPTER 7

Appendix table 7.1: HCV transmission parameters* among the general population and people who inject drugs (PWID).

Country	Transmission parameters (95% credibility intervals)	
	General population (β)	PWID (θ)
Kazakhstan	0.0012 (0.0000, 0.0270)	0.5549 (0.4409, 0.9079)
Kyrgyzstan	0.0365 (0.0041, 0.0607)	0.4676 (0.3592, 0.8775)
Tajikistan	0.0515 (0.0173, 0.0786)	0.5958 (0.4466, 1.0845)
Turkmenistan	0.0443 (0.0179, 0.0692)	0.5559 (0.4063, 1.0192)
Uzbekistan	0.0381 (0.0089, 0.0656)	0.4587 (0.3312, 0.8418)
Armenia	0.0085 (0.0000, 0.0224)	0.3014 (0.2379, 0.4369)
Azerbaijan	0.0235 (0.0070, 0.0411)	0.4361 (0.3471, 0.6763)
Belarus	0.0019 (0.0000, 0.0182)	0.4146 (0.3436, 0.5666)
Bosnia	0.0000 (0.0000, 0.0031)	0.3202 (0.2831, 0.3932)
Bulgaria	0.0000 (0.0000, 0.0142)	0.4215 (0.3515, 0.6085)
Czech Republic	0.0116 (0.0000, 0.0275)	0.2702 (0.2264, 0.3999)
Estonia	0.0000 (0.0000, 0.0072)	0.4185 (0.3583, 0.5157)
Georgia	0.0000 (0.0000, 0.0160)	0.3034 (0.2468, 0.4038)
Hungary	0.0173 (0.0028, 0.0327)	0.3356 (0.2639, 0.5363)
Latvia	0.0000 (0.0000, 0.0103)	0.4341 (0.3488, 0.5445)
Lithuania	0.0067 (0.0000, 0.0217)	0.3155 (0.2648, 0.4786)
Moldova	0.0133 (0.0000, 0.0283)	0.3258 (0.2595, 0.4624)
Poland	0.0083 (0.0000, 0.0245)	0.3526 (0.3083, 0.4869)
Romania	0.0000 (0.0000, 0.0144)	0.5035 (0.3877, 0.6627)
Russia	0.0000 (0.0000, 0.0141)	0.4163 (0.3474, 0.5627)
Slovakia	0.0062 (0.0000, 0.0229)	0.3482 (0.2794, 0.4923)
Ukraine	0.0000 (0.0000, 0.0140)	0.2344 (0.1806, 0.3665)
Australia	0.0215 (0.0035, 0.0359)	0.2375 (0.1882, 0.3864)
New Zealand	0.0135 (0.0000, 0.0288)	0.3142 (0.2412, 0.4764)
China	0.0166 (0.0000, 0.0344)	0.3604 (0.2618, 0.6583)
Indonesia	0.0164 (0.0000, 0.0365)	0.6285 (0.4898, 1.1142)
Japan	0.0000 (0.0000, 0.0151)	0.3690 (0.2867, 0.5806)
Malaysia	0.0264 (0.0000, 0.0475)	0.3393 (0.2756, 0.5183)
Myanmar	0.0127 (0.0000, 0.0328)	0.5381 (0.4001, 1.0930)
Philippines	0.0346 (0.0140, 0.0522)	0.3880 (0.2869, 0.7131)
Taiwan	0.0091 (0.0000, 0.0284)	0.3605 (0.2742, 0.6109)
Thailand	0.0182 (0.0000, 0.0375)	0.5718 (0.4270, 1.0401)
Viet Nam	0.0189 (0.0000, 0.0365)	0.4905 (0.3518, 0.9202)
Afghanistan	0.0422 (0.0018, 0.0647)	0.3912 (0.2958, 0.6647)
Bangladesh	0.0293 (0.0149, 0.0449)	0.3526 (0.2582, 0.6167)
India	0.0329 (0.0187, 0.0471)	0.3300 (0.2521, 0.5846)
Iran	0.0107 (0.0000, 0.0281)	0.3437 (0.2578, 0.5785)
Nepal	0.0190 (0.0000, 0.0351)	0.4520 (0.3206, 0.8031)
Pakistan	0.0395 (0.0224, 0.0552)	0.3894 (0.1510, 0.8511)
Canada	0.0130 (0.0000, 0.0283)	0.3449 (0.2390, 0.5760)
USA	0.0173 (0.0000, 0.0342)	0.2002 (0.1526, 0.3445)
Albania	0.0066 (0.0000, 0.0195)	0.2095 (0.1585, 0.3493)
Austria	0.0000 (0.0000, 0.0155)	0.2679 (0.2157, 0.4166)
Belgium	0.0000 (0.0000, 0.0211)	0.2595 (0.1836, 0.4671)
Croatia	0.0076 (0.0000, 0.0215)	0.2179 (0.1690, 0.3515)
Cyprus	0.0233 (0.0043, 0.0404)	0.3175 (0.2354, 0.5717)
Denmark	0.0039 (0.0000, 0.0200)	0.1792 (0.1419, 0.2760)
FYROM	0.0009 (0.0000, 0.0168)	0.3069 (0.2446, 0.4949)
Finland	0.0000 (0.0000, 0.0078)	0.2910 (0.2415, 0.4114)
France	0.0035 (0.0000, 0.0206)	0.2794 (0.2133, 0.5294)

Country	Transmission parameters (95% credibility intervals)	
	General population (β)	PWID (θ)
Germany	0.0068 (0.0000, 0.0251)	0.2758 (0.2134, 0.4547)
Greece	0.0197 (0.0036, 0.0348)	0.3000 (0.2315, 0.5252)
Iceland	0.0000 (0.0000, 0.0173)	0.4142 (0.3355, 0.6434)
Ireland	0.0128 (0.0000, 0.0297)	0.3445 (0.2739, 0.5643)
Italy	0.0000 (0.0000, 0.0161)	0.2615 (0.1652, 0.4608)
Luxembourg	0.0078 (0.0000, 0.0288)	0.3922 (0.3053, 0.5833)
Malta	0.0093 (0.0000, 0.0262)	0.2012 (0.1517, 0.3426)
Montenegro	0.0000 (0.0000, 0.0119)	0.3467 (0.2663, 0.6136)
Netherlands	0.0196 (0.0032, 0.0356)	0.2675 (0.2062, 0.4653)
Norway	0.0121 (0.0000, 0.0279)	0.2895 (0.2267, 0.4639)
Portugal	0.0000 (0.0000, 0.0171)	0.4132 (0.2976, 0.7454)
Serbia	0.0000 (0.0000, 0.0053)	0.2280 (0.1865, 0.3367)
Slovenia	0.0028 (0.0000, 0.0206)	0.2069 (0.1611, 0.3256)
Spain	0.0250 (0.0081, 0.0401)	0.3389 (0.2622, 0.5964)
Sweden	0.0151 (0.0000, 0.0371)	0.3409 (0.2737, 0.5077)
Switzerland	0.0080 (0.0000, 0.0260)	0.3226 (0.2439, 0.5766)
UK	0.0027 (0.0000, 0.0221)	0.4220 (0.3515, 0.5903)
Ghana	0.0507 (0.0344, 0.0678)	0.3440 (0.2786, 0.5063)
Kenya	0.0424 (0.0232, 0.0612)	0.4664 (0.3733, 0.7531)
Madagascar	0.0525 (0.0330, 0.0709)	0.2679 (0.1444, 0.4235)
Mauritius	0.0063 (0.0000, 0.0255)	0.5430 (0.4808, 0.7071)
Mozambique	0.0457 (0.0233, 0.0658)	0.5539 (0.4480, 0.8560)
Nigeria	0.0554 (0.0374, 0.0737)	0.1533 (0.0672, 0.2790)
Senegal	0.0569 (0.0376, 0.0757)	0.4350 (0.3485, 0.6628)
Tanzania	0.0476 (0.0112, 0.0682)	0.4446 (0.2958, 0.8229)
Argentina	0.0178 (0.0003, 0.0332)	0.2851 (0.2310, 0.4611)
Brazil	0.0114 (0.0000, 0.0275)	0.3256 (0.2664, 0.4884)
Mexico	0.0196 (0.0018, 0.0359)	0.5666 (0.4646, 0.8733)
Uruguay	0.0144 (0.0000, 0.0294)	0.1693 (0.1351, 0.2912)
Egypt	0.0412 (0.0214, 0.0593)	0.3221 (0.2065, 0.6465)
Israel	0.0366 (0.0179, 0.0528)	0.2428 (0.1961, 0.4018)
Lebanon	0.0414 (0.0108, 0.0602)	0.4069 (0.3018, 0.7549)
Libya	0.0219 (0.0031, 0.0381)	0.9148 (0.6745, 1.6960)
Morocco	0.0247 (0.0064, 0.0407)	0.3450 (0.2528, 0.5824)
Saudi Arabia	0.0092 (0.0000, 0.0345)	0.6855 (0.5189, 1.1848)
Syria	0.0359 (0.0179, 0.0539)	0.5669 (0.3980, 1.0766)
Tunisia	0.0076 (0.0000, 0.0273)	0.4432 (0.3156, 0.8650)
Turkey	0.0055 (0.0000, 0.0273)	0.5272 (0.3984, 0.9477)

*The transmission parameters for the general population (β) and PWID (θ) are used to calculate the transmission rates through multiplication with the HCV prevalences in the respective populations; see the appendix.

Appendix table 7.2: Percentage differences between target prevalences and fitted values.

	Median (95% credibility intervals), to 4 decimal places		
Country	**Adult % PWID**	**PWID % chronic HCV**	**Gen-pop % chronic HCV**
Overall	**0.0000 (0.0000, 0.0000)**	**0.0000 (0.0000, 23.1888)**	**0.0000 (0.0000, 19.5878)**
Kazakhstan	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 30.3155)	0.0000 (0.0000, 4.3707)
Kyrgyzstan	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Tajikistan	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Turkmenistan	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Uzbekistan	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Armenia	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 24.2182)	0.0000 (0.0000, 2.4835)
Azerbaijan	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Belarus	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 26.3122)	0.0000 (0.0000, 9.7487)
Bosnia	0.0000 (0.0000, 0.0000)	0.5768 (0.0000, 1.9393)	12.4833 (0.0000, 31.1541)
Bulgaria	0.0000 (0.0000, 0.0000)	1.3755 (0.0000, 25.4172)	0.9233 (0.0000, 16.8026)
Czech Republic	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 13.5840)	0.0000 (0.0000, 5.1109)
Estonia	0.0000 (0.0000, 0.0000)	15.957 (0.0000, 32.1406)	3.5712 (0.0000, 6.8400)
Georgia	0.0000 (0.0000, 0.0000)	5.2998 (0.0000, 30.2172)	0.0744 (0.0000, 0.4336)
Hungary	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0001)	0.0000 (0.0000, 0.0001)
Latvia	0.0000 (0.0000, 0.0000)	8.0438 (0.0000, 31.3363)	1.7592 (0.0000, 6.5260)
Lithuania	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 17.7356)	0.0000 (0.0000, 10.1816)
Moldova	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 7.8567)	0.0000 (0.0000, 2.1969)
Poland	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 6.1191)	0.0000 (0.0000, 10.6574)
Romania	0.0000 (0.0000, 0.0000)	1.6976 (0.0000, 30.0756)	0.3841 (0.0000, 7.9480)
Russia	0.0000 (0.0000, 0.0000)	11.4323 (0.0000, 32.0523)	0.7320 (0.0000, 3.7018)
Slovakia	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 17.6179)	0.0000 (0.0000, 8.0233)
Ukraine	0.0000 (0.0000, 0.0000)	0.0677 (0.0000, 31.3127)	0.0082 (0.0000, 5.7633)
Australia	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0003)	0.0000 (0.0000, 0.0004)
New Zealand	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 14.3745)	0.0000 (0.0000, 6.2953)
China	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 5.2793)	0.0000 (0.0000, 2.7310)
Indonesia	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 2.0484)	0.0000 (0.0000, 12.7867)
Japan	0.0000 (0.0000, 0.0000)	6.2041 (0.0000, 30.4503)	3.8911 (0.0000, 22.0100)
Malaysia	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 23.9627)	0.0000 (0.0000, 9.4064)
Myanmar	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 26.3299)	0.0000 (0.0000, 2.8791)
Philippines	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Taiwan	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 10.9844)	0.0000 (0.0000, 6.7234)
Thailand	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 2.3005)	0.0000 (0.0000, 3.8096)
Viet Nam	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 3.1905)	0.0000 (0.0000, 1.4454)
Afghanistan	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.9701)	0.0000 (0.0000, 0.4177)
Bangladesh	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
India	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Iran	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 8.6769)	0.0000 (0.0000, 18.0241)
Nepal	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 2.5258)	0.0000 (0.0000, 3.4996)
Pakistan	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Canada	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 9.3889)	0.0000 (0.0000, 11.0014)
USA	0.0000 (0.0000, 0.0000)	5.0788 (0.3235, 11.5012)	19.7636 (0.9881, 32.3413)
Albania	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 25.6438)	0.0000 (0.0000, 5.9925)
Austria	0.0000 (0.0000, 0.0000)	1.1589 (0.0000, 12.6917)	4.3463 (0.0000, 29.3384)
Belgium	0.0000 (0.0000, 0.0000)	0.0027 (0.0000, 3.7323)	0.0060 (0.0000, 10.1140)
Croatia	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 8.5050)	0.0000 (0.0000, 8.2879)
Cyprus	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Denmark	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 13.5931)	0.0000 (0.0000, 15.3433)
FYROM	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 5.3951)	0.0000 (0.0000, 22.0363)
Finland	0.0000 (0.0000, 0.0000)	6.3568 (0.0000, 28.0295)	9.3372 (0.0000, 28.9889)

Country	Adult % PWID	PWID % chronic HCV	Gen-pop % chronic HCV
France	0.0000 (0.0000, 0.0000)	2.4406 (0.0898, 11.7872)	12.1664 (0.6639, 31.1497)
Germany	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 10.9042)	0.0001 (0.0000, 24.2749)
Greece	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0002)	0.0000 (0.0000, 0.0002)
Iceland	0.0000 (0.0000, 0.0000)	1.3938 (0.0000, 13.3933)	5.2428 (0.0000, 31.048)
Ireland	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 4.9363)	0.0000 (0.0000, 9.1627)
Italy	0.0000 (0.0000, 0.0000)	3.1544 (0.0000, 31.5321)	0.4526 (0.0000, 6.4067)
Luxembourg	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 18.3903)	0.0000 (0.0000, 16.6488)
Malta	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 6.8324)	0.0000 (0.0000, 11.0054)
Montenegro	0.0000 (0.0000, 0.0000)	6.4577 (0.0000, 30.9746)	3.1795 (0.0000, 14.3764)
Netherlands	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Norway	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 5.4320)	0.0000 (0.0000, 12.1772)
Portugal	0.0000 (0.0000, 0.0000)	0.2116 (0.0000, 3.5705)	0.5945 (0.0000, 8.8305)
Serbia	0.0000 (0.0000, 0.0000)	11.5035 (0.0000, 31.1178)	8.4594 (0.0000, 20.0265)
Slovenia	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 23.4785)	0.0000 (0.0000, 19.5172)
Spain	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0002)	0.0000 (0.0000, 0.0002)
Sweden	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 24.6035)	0.0000 (0.0000, 17.9099)
Switzerland	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 3.3232)	0.0000 (0.0000, 6.5402)
UK	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 11.5702)	0.0000 (0.0000, 16.8252)
Ghana	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Kenya	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Madagascar	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Mauritius	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 26.2514)	0.0000 (0.0000, 7.1136)
Mozambique	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Nigeria	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Senegal	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Tanzania	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Argentina	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.3733)	0.0000 (0.0000, 0.4496)
Brazil	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 12.8522)	0.0000 (0.0000, 6.1677)
Mexico	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Uruguay	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 2.8755)	0.0000 (0.0000, 0.8262)
Egypt	0.0000 (0.0000, 0.0000)	9.6947 (4.5902, 16.2080)	12.1368 (0.7298, 29.0261)
Israel	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Lebanon	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Libya	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Morocco	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Saudi Arabia	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 12.3862)	0.0000 (0.0000, 27.4478)
Syria	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Tunisia	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 5.2494)	0.0000 (0.0000, 7.0606)
Turkey	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 28.0645)	0.0000 (0.0000, 10.8709)

Gen-pop: General population; PWID: People who inject drugs; HCV: Hepatitis C virus

Appendix table 7.3: Prior and posterior distributions of the general population HCV prevalence, PWID HCV prevalence, and the percentage of adults that are PWID.

	General population HCV prevalence Median (minimum, maximum)		PWID HCV prevalence Median (minimum, maximum)		Adult % PWID Median (minimum, maximum)	
Country	**Prior**	**Posterior**	**Prior**	**Posterior**	**Prior**	**Posterior**
Afghanistan	0.89% (0.33%, 1.54%)	0.90% (0.35%, 1.54%)	29.7% (21.3%, 38.4%)	29.7% (21.3%, 38.4%)	0.80% (0.52%, 1.08%)	0.80% (0.52%, 1.08%)
Albania	2.13% (1.39%, 2.91%)	2.14% (1.43%, 2.91%)	24.3% (19.1%, 30.2%)	23.8% (13.6%, 29.0%)	0.42% (0.29%, 0.55%)	0.42% (0.29%, 0.55%)
Argentina	0.98% (0.25%, 1.53%)	0.99% (0.28%, 1.53%)	40.4% (36.5%, 44.3%)	40.3% (36.5%, 44.2%)	0.29% (0.29%, 0.30%)	0.29% (0.29%, 0.30%)
Armenia	2.77% (1.85%, 3.78%)	2.77% (1.95%, 3.78%)	29.7% (20.6%, 40.0%)	29.3% (16.7%, 39.0%)	0.77% (0.41%, 1.34%)	0.76% (0.42%, 1.33%)
Australia	1.07% (0.87%, 1.41%)	1.07% (0.90%, 1.41%)	40.1% (36.5%, 43.7%)	40.1% (35.6%, 43.5%)	0.60% (0.44%, 0.75%)	0.60% (0.44%, 0.75%)
Austria	0.32% (0.08%, 0.50%)	0.35% (0.13%, 0.55%)	43.2% (38.2%, 49.0%)	42.2% (33.5%, 48.6%)	0.32% (0.22%, 0.42%)	0.31% (0.22%, 0.41%)
Azerbaijan	2.58% (1.70%, 3.52%)	2.58% (1.70%, 3.45%)	43.2% (32.7%, 54.1%)	43.3% (32.9%, 53.9%)	0.61% (0.49%, 0.74%)	0.62% (0.50%, 0.74%)
Bangladesh	0.98% (0.17%, 1.76%)	1.01% (0.17%, 1.73%)	26.7% (17.5%, 36.2%)	26.6% (17.6%, 35.5%)	0.07% (0.06%, 0.07%)	0.07% (0.06%, 0.07%)
Belarus	1.11% (0.59%, 2.02%)	1.13% (0.62%, 1.97%)	40.5% (29.7%, 51.8%)	38.7% (23.5%, 51.2%)	0.59% (0.23%, 0.95%)	0.59% (0.23%, 0.95%)
Belgium	0.51% (0.10%, 0.79%)	0.52% (0.14%, 0.79%)	41.4% (32.8%, 50.3%)	41.2% (32.4%, 49.7%)	0.36% (0.24%, 0.49%)	0.36% (0.24%, 0.49%)
Bosnia	0.07% (0.05%, 0.09%)	0.08% (0.05%, 0.11%)	27.8% (19.0%, 37.2%)	27.4% (18.9%, 36.5%)	0.17% (0.11%, 0.22%)	0.17% (0.11%, 0.22%)
Brazil	1.02% (0.81%, 1.23%)	1.02% (0.81%, 1.23%)	47.3% (43.3%, 51.3%)	47.0% (34.5%, 51.1%)	0.68% (0.51%, 0.87%)	0.68% (0.52%, 0.86%)
Bulgaria	1.06% (0.50%, 1.72%)	1.08% (0.53%, 1.77%)	47.7% (43.1%, 52.5%)	46.2% (31.6%, 52.0%)	0.38% (0.30%, 0.45%)	0.38% (0.30%, 0.45%)
Canada	0.73% (0.47%, 1.02%)	0.74% (0.48%, 1.02%)	56.1% (44.2%, 72.4%)	55.7% (42.0%, 71.1%)	0.39% (0.31%, 0.47%)	0.39% (0.31%, 0.47%)
China	0.77% (0.58%, 0.98%)	0.77% (0.59%, 0.98%)	27.3% (17.1%, 38.0%)	27.2% (17.1%, 37.4%)	0.25% (0.19%, 0.31%)	0.25% (0.19%, 0.31%)
Croatia	0.66% (0.36%, 1.01%)	0.66% (0.39%, 1.03%)	26.1% (19.7%, 33.1%)	25.9% (18.7%, 32.7%)	0.23% (0.18%, 0.29%)	0.23% (0.18%, 0.29%)
Cyprus	0.64% (0.32%, 1.33%)	0.64% (0.32%, 1.31%)	35.2% (30.6%, 40.1%)	35.3% (31.2%, 39.7%)	0.08% (0.04%, 0.12%)	0.08% (0.04%, 0.12%)
Czech Republic	0.35% (0.14%, 0.49%)	0.35% (0.15%, 0.50%)	12.8% (9.9%, 16.0%)	12.6% (8.6%, 15.5%)	0.64% (0.61%, 0.67%)	0.64% (0.61%, 0.67%)
Denmark	0.43% (0.33%, 0.52%)	0.44% (0.33%, 0.58%)	30.2% (25.2%, 35.7%)	29.7% (21.2%, 35.5%)	0.44% (0.35%, 0.52%)	0.44% (0.35%, 0.52%)
Egypt	6.88% (6.33%, 7.49%)	7.73% (6.57%, 9.79%)	34.0% (24.2%, 44.4%)	30.7% (20.5%, 41.0%)	0.21% (0.13%, 0.28%)	0.21% (0.14%, 0.28%)
Estonia	1.28% (1.03%, 1.46%)	1.32% (1.04%, 1.49%)	55.0% (45.3%, 64.6%)	46.1% (32.3%, 62.4%)	1.09% (0.71%, 1.72%)	1.08% (0.71%, 1.71%)
FYROM	0.36% (0.24%, 0.48%)	0.37% (0.24%, 0.54%)	44.1% (40.9%, 47.7%)	43.8% (38.9%, 47.4%)	0.16% (0.11%, 0.21%)	0.16% (0.11%, 0.21%)
Finland	0.51% (0.42%, 0.66%)	0.57% (0.44%, 0.76%)	52.2% (47.5%, 56.9%)	48.6% (33.9%, 55.9%)	0.50% (0.41%, 0.67%)	0.50% (0.41%, 0.67%)

	General population HCV prevalence Median (minimum, maximum)		PWID HCV prevalence Median (minimum, maximum)		Adult % PWID Median (minimum, maximum)	
Country	**Prior**	**Posterior**	**Prior**	**Posterior**	**Prior**	**Posterior**
France	0.57% (0.32%, 0.80%)	0.63% (0.42%, 0.87%)	45.4% (41.5%, 49.1%)	46.2% (40.1%, 53.6%)	0.20% (0.16%, 0.23%)	0.20% (0.16%, 0.23%)
Georgia	5.40% (4.56%, 6.35%)	5.41% (4.58%, 6.29%)	48.0% (39.0%, 57.2%)	44.3% (29.0%, 57.0%)	4.26% (0.61%, 7.81%)	4.23% (0.70%, 7.81%)
Germany	0.42% (0.21%, 0.65%)	0.43% (0.22%, 0.65%)	46.1% (41.2%, 51.2%)	45.7% (36.9%, 50.5%)	0.24% (0.03%, 0.45%)	0.23% (0.04%, 0.44%)
Ghana	1.96% (0.85%, 3.86%)	1.91% (0.88%, 3.79%)	28.2% (23.8%, 32.9%)	28.2% (24.0%, 32.9%)	0.05% (0.03%, 0.07%)	0.05% (0.03%, 0.07%)
Greece	1.17% (0.35%, 1.85%)	1.17% (0.39%, 1.83%)	46.7% (42.3%, 51.2%)	46.6% (42.3%, 51.2%)	0.07% (0.06%, 0.09%)	0.07% (0.06%, 0.09%)
Hungary	0.82% (0.28%, 1.89%)	0.84% (0.28%, 1.89%)	32.4% (21.1%, 45.3%)	32.6% (21.4%, 44.3%)	0.06% (0.03%, 0.08%)	0.06% (0.03%, 0.08%)
Iceland	0.29% (0.23%, 0.35%)	0.31% (0.24%, 0.44%)	44.7% (40.8%, 48.4%)	43.6% (35.5%, 48.4%)	0.24% (0.16%, 0.32%)	0.24% (0.16%, 0.32%)
India	0.72% (0.40%, 1.18%)	0.73% (0.40%, 1.18%)	31.3% (26.0%, 36.7%)	31.4% (26.0%, 36.5%)	0.02% (0.01%, 0.03%)	0.02% (0.01%, 0.03%)
Indonesia	0.55% (0.08%, 1.08%)	0.55% (0.11%, 1.07%)	56.5% (52.2%, 61.3%)	56.4% (52.3%, 60.9%)	0.11% (0.09%, 0.13%)	0.11% (0.09%, 0.13%)
Iran	0.44% (0.15%, 0.79%)	0.44% (0.17%, 0.79%)	34.7% (21.8%, 47.8%)	34.3% (21.8%, 46.4%)	0.28% (0.19%, 0.37%)	0.28% (0.19%, 0.37%)
Ireland	0.68% (0.47%, 1.14%)	0.68% (0.47%, 1.13%)	52.9% (49.0%, 56.8%)	52.8% (46.6%, 56.8%)	0.27% (0.20%, 0.33%)	0.27% (0.20%, 0.33%)
Israel	1.16% (0.61%, 1.50%)	1.15% (0.65%, 1.47%)	31.2% (25.6%, 37.0%)	31.2% (25.6%, 37.0%)	0.41% (0.28%, 0.54%)	0.41% (0.28%, 0.54%)
Italy	2.54% (1.17%, 5.29%)	2.58% (1.26%, 5.15%)	41.1% (36.0%, 46.5%)	38.9% (25.7%, 46.0%)	0.85% (0.57%, 1.13%)	0.85% (0.57%, 1.12%)
Japan	0.75% (0.31%, 1.39%)	0.79% (0.38%, 1.46%)	41.1% (34.3%, 48.6%)	38.1% (24.4%, 46.9%)	0.47% (0.36%, 0.58%)	0.47% (0.36%, 0.58%)
Kazakhstan	1.43% (0.63%, 2.16%)	1.48% (0.71%, 2.16%)	28.6% (25.0%, 32.8%)	27.3% (17.3%, 31.9%)	1.00% (0.65%, 1.42%)	0.99% (0.65%, 1.38%)
Kenya	0.47% (0.15%, 0.72%)	0.48% (0.16%, 0.72%)	11.8% (7.6%, 16.7%)	11.8% (7.7%, 16.5%)	0.12% (0.03%, 0.20%)	0.12% (0.04%, 0.20%)
Kyrgyzstan	1.66% (0.77%, 3.29%)	1.69% (0.82%, 3.19%)	21.4% (18.7%, 24.1%)	21.4% (15.1%, 24.0%)	0.77% (0.51%, 1.10%)	0.77% (0.51%, 1.10%)
Latvia	1.70% (1.18%, 2.30%)	1.75% (1.26%, 2.33%)	51.7% (45.1%, 58.1%)	47.3% (31.7%, 57.4%)	0.93% (0.73%, 1.17%)	0.93% (0.74%, 1.15%)
Lebanon	0.22% (0.08%, 0.49%)	0.22% (0.08%, 0.47%)	16.3% (10.5%, 23.3%)	16.4% (10.7%, 22.9%)	0.14% (0.09%, 0.19%)	0.14% (0.09%, 0.19%)
Libya	0.83% (0.74%, 0.92%)	0.83% (0.74%, 0.92%)	64.8% (60.3%, 69.1%)	64.9% (60.3%, 69.0%)	0.05% (0.01%, 0.10%)	0.05% (0.01%, 0.10%)
Lithuania	1.35% (0.83%, 1.93%)	1.36% (0.87%, 2.02%)	28.6% (25.6%, 31.5%)	28.3% (19.8%, 31.2%)	0.23% (0.12%, 0.34%)	0.22% (0.12%, 0.33%)
Luxembourg	0.85% (0.40%, 1.17%)	0.85% (0.43%, 1.20%)	57.6% (52.5%, 62.8%)	56.9% (41.6%, 62.1%)	0.57% (0.45%, 0.69%)	0.57% (0.45%, 0.68%)
Madagascar	0.86% (0.53%, 1.24%)	0.85% (0.53%, 1.22%)	3.9% (1.6%, 6.4%)	3.9% (1.6%, 6.3%)	0.22% (0.02%, 0.58%)	0.22% (0.03%, 0.58%)
Malaysia	1.91% (0.20%, 4.82%)	1.87% (0.45%, 4.78%)	42.6% (38.3%, 46.9%)	42.4% (28.9%, 46.9%)	1.33% (1.12%, 1.55%)	1.33% (1.13%, 1.55%)
Malta	0.28% (0.19%, 0.43%)	0.29% (0.19%, 0.43%)	17.9% (9.3%, 26.9%)	20.0% (13.7%, 26.9%)	0.26% (0.18%, 0.35%)	0.27% (0.18%, 0.35%)
Mauritius	1.48% (0.98%, 2.04%)	1.50% (0.98%, 2.04%)	68.4% (64.7%, 72.2%)	67.7% (45.9%, 71.8%)	0.87% (0.40%, 1.52%)	0.86% (0.42%, 1.50%)

	General population HCV prevalence Median (minimum, maximum)		PWID HCV prevalence Median (minimum, maximum)		Adult % PWID Median (minimum, maximum)	
Country	**Prior**	**Posterior**	**Prior**	**Posterior**	**Prior**	**Posterior**
Mexico	1.02% (0.81%, 1.21%)	1.02% (0.81%, 1.25%)	70.6% (66.4%, 74.9%)	70.6% (66.7%, 74.9%)	0.18% (0.12%, 0.25%)	0.18% (0.12%, 0.25%)
Moldova	2.66% (1.58%, 3.25%)	2.67% (1.65%, 3.31%)	34.8% (23.2%, 47.0%)	34.7% (23.2%, 46.5%)	0.40% (0.25%, 0.54%)	0.39% (0.26%, 0.54%)
Montenegro	0.85% (0.57%, 1.15%)	0.88% (0.58%, 1.21%)	30.8% (27.3%, 34.5%)	28.6% (19.5%, 34.5%)	0.40% (0.27%, 0.53%)	0.39% (0.27%, 0.52%)
Morocco	0.95% (0.74%, 1.34%)	0.96% (0.75%, 1.33%)	37.2% (22.9%, 51.5%)	37.5% (24.0%, 50.9%)	0.13% (0.07%, 0.20%)	0.13% (0.07%, 0.20%)
Mozambique	1.79% (0.11%, 4.95%)	1.78% (0.14%, 4.95%)	47.3% (42.5%, 51.7%)	47.2% (42.5%, 51.6%)	0.20% (0.00%, 0.41%)	0.20% (0.00%, 0.41%)
Myanmar	1.11% (0.60%, 1.75%)	1.10% (0.60%, 1.67%)	18.8% (16.6%, 21.4%)	18.6% (11.9%, 21.3%)	0.48% (0.33%, 0.64%)	0.48% (0.33%, 0.64%)
Nepal	0.50% (0.33%, 0.68%)	0.50% (0.34%, 0.68%)	35.0% (23.5%, 46.1%)	34.7% (24.3%, 46.0%)	0.20% (0.19%, 0.21%)	0.20% (0.19%, 0.21%)
Netherlands	0.16% (0.05%, 0.27%)	0.16% (0.06%, 0.27%)	39.2% (34.4%, 44.8%)	39.2% (34.5%, 44.8%)	0.03% (0.02%, 0.04%)	0.03% (0.02%, 0.04%)
New Zealand	1.09% (0.61%, 1.62%)	1.10% (0.61%, 1.61%)	53.8% (46.6%, 61.8%)	53.3% (38.4%, 61.0%)	0.73% (0.50%, 0.96%)	0.73% (0.51%, 0.96%)
Nigeria	1.59% (1.43%, 1.83%)	1.59% (1.44%, 1.81%)	4.2% (2.5%, 6.3%)	4.2% (2.5%, 6.3%)	0.35% (0.24%, 0.46%)	0.35% (0.24%, 0.46%)
Norway	0.40% (0.31%, 0.51%)	0.40% (0.32%, 0.56%)	45.9% (41.1%, 50.9%)	45.7% (38.7%, 50.9%)	0.25% (0.21%, 0.29%)	0.25% (0.21%, 0.29%)
Pakistan	3.82% (3.55%, 4.14%)	3.82% (3.56%, 4.11%)	30.6% (4.7%, 62.0%)	30.1% (5.2%, 62.0%)	0.37% (0.32%, 0.42%)	0.37% (0.32%, 0.42%)
Philippines	0.68% (0.22%, 1.28%)	0.68% (0.22%, 1.28%)	22.1% (10.5%, 35.6%)	22.1% (10.5%, 35.6%)	0.04% (0.03%, 0.05%)	0.04% (0.03%, 0.05%)
Poland	0.60% (0.40%, 0.81%)	0.60% (0.40%, 0.81%)	41.6% (36.9%, 47.6%)	41.5% (36.4%, 47.6%)	0.27% (0.18%, 0.36%)	0.27% (0.18%, 0.36%)
Portugal	1.13% (0.35%, 2.05%)	1.16% (0.39%, 2.08%)	62.3% (55.1%, 69.3%)	61.7% (54.6%, 69.2%)	0.22% (0.19%, 0.25%)	0.22% (0.19%, 0.25%)
Romania	2.25% (1.99%, 2.55%)	2.29% (2.02%, 2.74%)	58.4% (54.0%, 63.3%)	56.2% (39.0%, 62.3%)	0.64% (0.47%, 0.83%)	0.64% (0.47%, 0.83%)
Russia	2.59% (0.83%, 3.93%)	2.70% (0.90%, 3.91%)	47.8% (40.2%, 55.5%)	42.1% (28.5%, 54.5%)	1.79% (0.95%, 2.67%)	1.76% (0.97%, 2.66%)
Saudi Arabia	0.35% (0.27%, 0.43%)	0.36% (0.28%, 0.52%)	53.4% (48.5%, 58.3%)	52.9% (41.8%, 57.6%)	0.20% (0.13%, 0.27%)	0.20% (0.13%, 0.27%)
Senegal	1.20% (0.02%, 3.27%)	1.23% (0.02%, 3.20%)	27.6% (21.6%, 34.4%)	27.6% (21.6%, 34.4%)	0.08% (0.05%, 0.11%)	0.08% (0.05%, 0.11%)
Serbia	0.36% (0.23%, 0.48%)	0.38% (0.26%, 0.55%)	18.4% (15.2%, 21.8%)	16.2% (11.4%, 20.8%)	0.49% (0.41%, 0.58%)	0.49% (0.41%, 0.58%)
Slovakia	0.99% (0.60%, 1.40%)	1.00% (0.62%, 1.43%)	38.9% (24.8%, 53.8%)	37.8% (22.0%, 53.2%)	0.56% (0.35%, 0.88%)	0.56% (0.35%, 0.88%)
Slovenia	0.28% (0.21%, 0.36%)	0.29% (0.21%, 0.39%)	21.6% (18.2%, 25.3%)	20.9% (14.2%, 24.8%)	0.42% (0.30%, 0.55%)	0.42% (0.30%, 0.55%)
Spain	1.06% (0.30%, 1.87%)	1.08% (0.29%, 1.83%)	50.4% (47.2%, 53.7%)	50.4% (47.2%, 57.4%)	0.07% (0.05%, 0.10%)	0.08% (0.05%, 0.10%)
Sweden	0.41% (0.33%, 0.50%)	0.41% (0.32%, 0.58%)	57.9% (54.1%, 61.6%)	57.9% (49.1%, 75.4%)	0.24% (0.04%, 0.61%)	0.23% (0.04%, 0.61%)
Switzerland	0.99% (0.57%, 1.27%)	1.01% (0.57%, 1.27%)	52.9% (47.6%, 58.5%)	52.7% (47.0%, 57.9%)	0.24% (0.19%, 0.29%)	0.24% (0.19%, 0.29%)
Syria	1.68% (0.43%, 2.58%)	1.71% (0.48%, 2.54%)	41.7% (27.9%, 56.6%)	41.6% (27.9%, 56.1%)	0.07% (0.04%, 0.09%)	0.07% (0.04%, 0.09%)

	General population HCV prevalence Median (minimum, maximum)		PWID HCV prevalence Median (minimum, maximum)		Adult % PWID Median (minimum, maximum)	
Country	**Prior**	**Posterior**	**Prior**	**Posterior**	**Prior**	**Posterior**
Taiwan	2.91% (1.56%, 5.53%)	2.96% (1.56%, 5.44%)	57.9% (54.4%, 61.5%)	57.6% (45.5%, 61.5%)	0.30% (0.20%, 0.40%)	0.30% (0.20%, 0.39%)
Tajikistan	1.71% (0.54%, 3.29%)	1.72% (0.55%, 3.28%)	29.9% (25.9%, 33.6%)	29.9% (26.2%, 33.6%)	0.47% (0.31%, 0.65%)	0.47% (0.31%, 0.65%)
Tanzania	2.43% (0.16%, 5.59%)	2.50% (0.20%, 5.45%)	19.6% (15.1%, 24.1%)	19.5% (12.4%, 23.7%)	1.24% (0.72%, 1.74%)	1.24% (0.72%, 1.74%)
Thailand	1.04% (0.48%, 2.36%)	1.03% (0.49%, 2.28%)	56.0% (50.7%, 61.9%)	55.8% (48.0%, 61.3%)	0.11% (0.03%, 0.18%)	0.11% (0.03%, 0.18%)
Tunisia	0.76% (0.16%, 1.21%)	0.75% (0.17%, 1.20%)	20.0% (17.1%, 23.2%)	19.9% (16.9%, 23.2%)	0.21% (0.14%, 0.29%)	0.21% (0.14%, 0.28%)
Turkey	0.80% (0.42%, 1.47%)	0.83% (0.44%, 1.42%)	30.9% (27.8%, 34.0%)	30.3% (19.9%, 33.9%)	0.42% (0.28%, 0.55%)	0.42% (0.29%, 0.55%)
Turkmenistan	2.28% (0.60%, 3.34%)	2.30% (0.65%, 3.34%)	29.5% (21.6%, 38.4%)	29.4% (22.9%, 37.5%)	0.40% (0.27%, 0.53%)	0.40% (0.28%, 0.53%)
UK	0.38% (0.27%, 0.53%)	0.39% (0.27%, 0.57%)	32.1% (21.5%, 43.3%)	31.5% (20.7%, 43.3%)	0.40% (0.38%, 0.42%)	0.40% (0.38%, 0.42%)
USA	1.01% (0.88%, 1.17%)	1.21% (0.84%, 1.52%)	40.2% (28.5%, 52.6%)	37.6% (25.4%, 52.6%)	1.31% (0.59%, 1.86%)	1.22% (0.62%, 1.84%)
Ukraine	2.19% (0.64%, 3.25%)	2.25% (0.70%, 3.21%)	38.3% (33.9%, 42.8%)	36.6% (23.6%, 42.6%)	1.07% (0.54%, 1.79%)	1.06% (0.55%, 1.73%)
Uruguay	0.74% (0.50%, 0.99%)	0.74% (0.51%, 0.99%)	16.2% (13.7%, 18.7%)	16.1% (10.7%, 18.7%)	0.40% (0.10%, 0.86%)	0.40% (0.10%, 0.85%)
Uzbekistan	5.45% (3.08%, 6.83%)	5.45% (3.22%, 6.69%)	25.2% (21.9%, 29.1%)	25.2% (19.0%, 29.1%)	0.49% (0.32%, 0.69%)	0.49% (0.32%, 0.69%)
Viet Nam	0.99% (0.75%, 1.31%)	0.99% (0.75%, 1.31%)	37.2% (26.6%, 48.2%)	37.1% (27.0%, 48.0%)	0.25% (0.19%, 0.31%)	0.25% (0.19%, 0.31%)

PWID: People who inject drugs; HCV: Hepatitis C virus

Appendix figure 7.1: Model runs showing time trends in the total population (top left), the percentage of the adult population that are people who inject drugs (top right), the prevalence of hepatitis C virus amongst the general population (bottom left), and the prevalence of hepatitis C virus amongst people who inject drugs (bottom right) for each country modelled. The black, vertical lines show the range of values that could be sampled.

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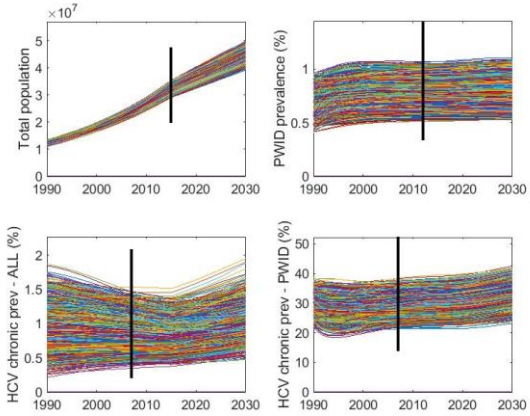
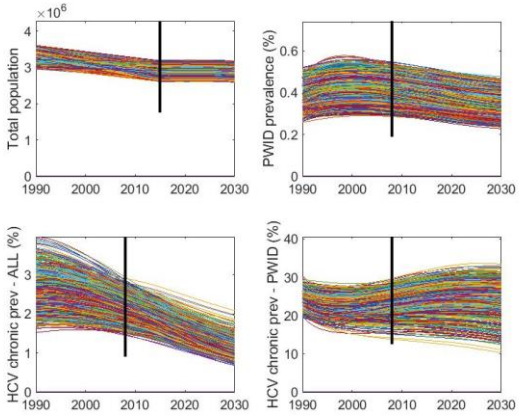


Albania



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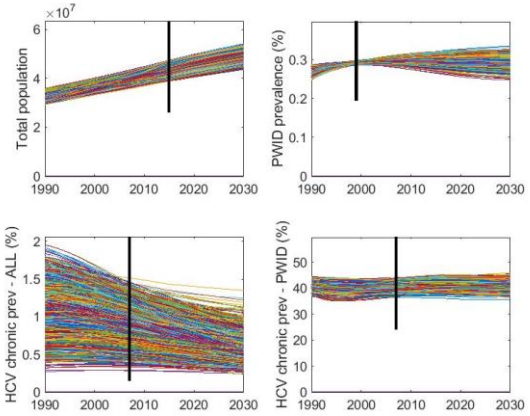

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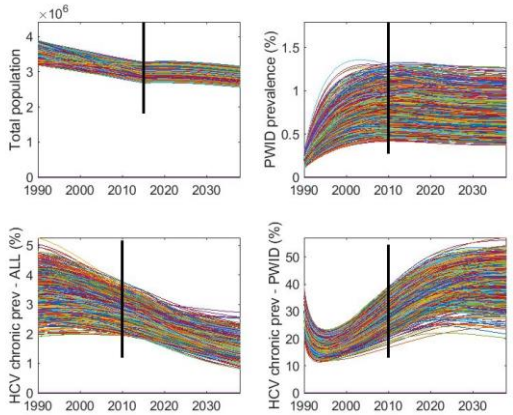

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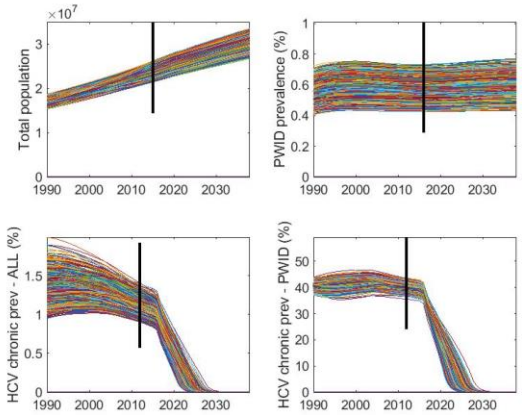

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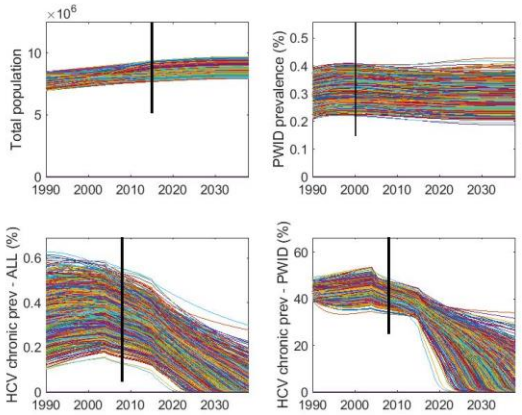

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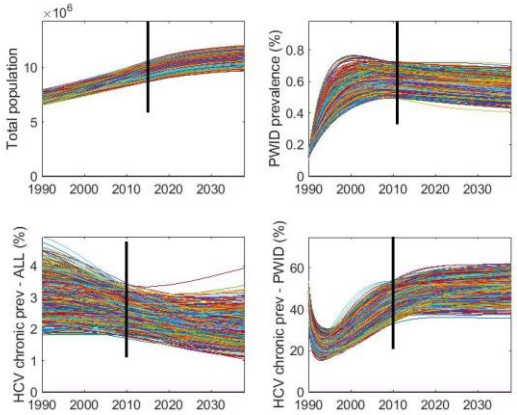

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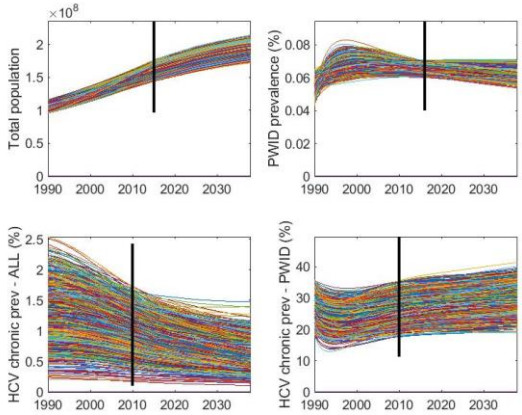

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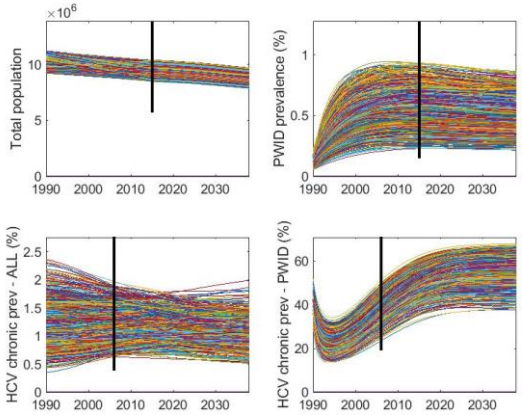

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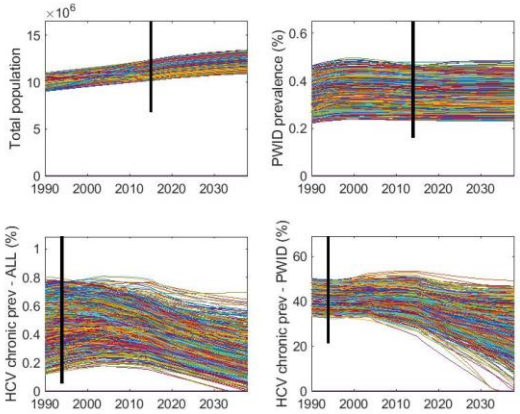
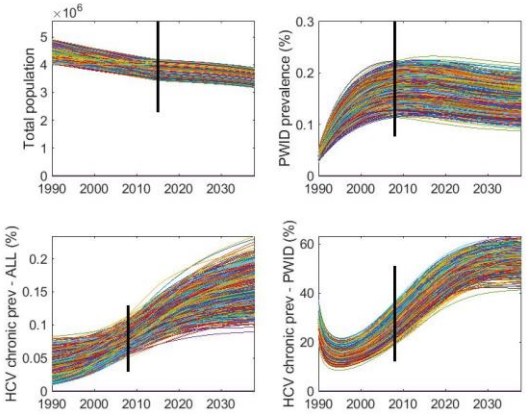


Bosnia Herzegovina



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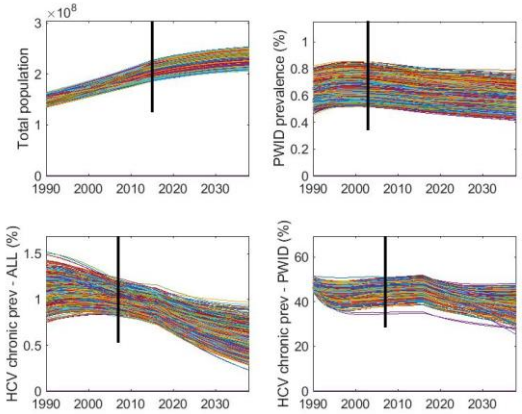

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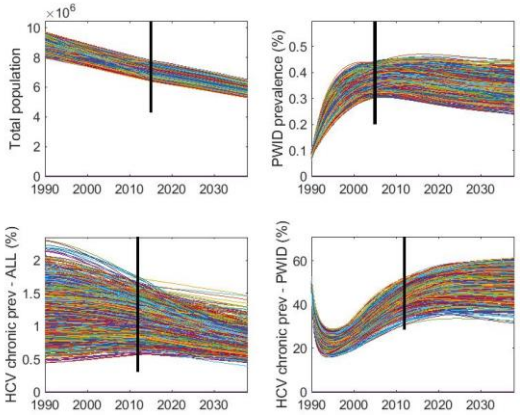

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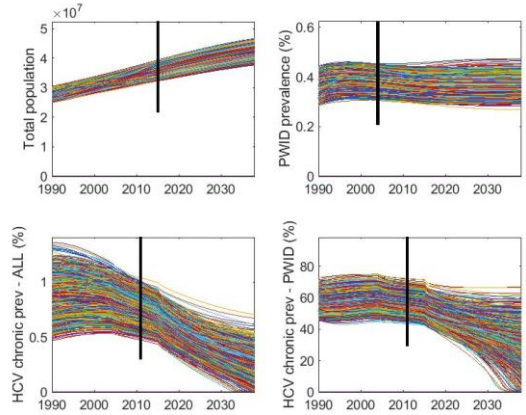

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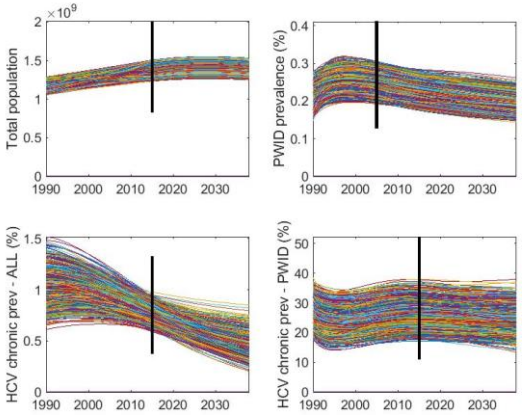

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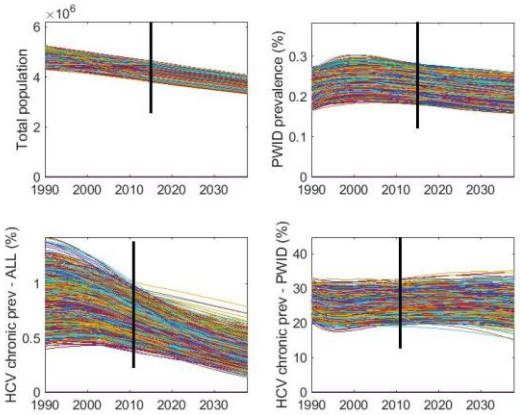

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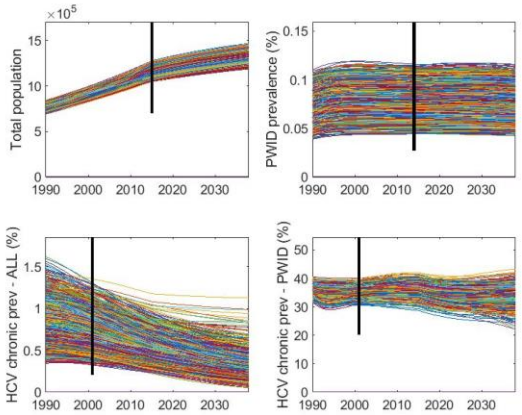

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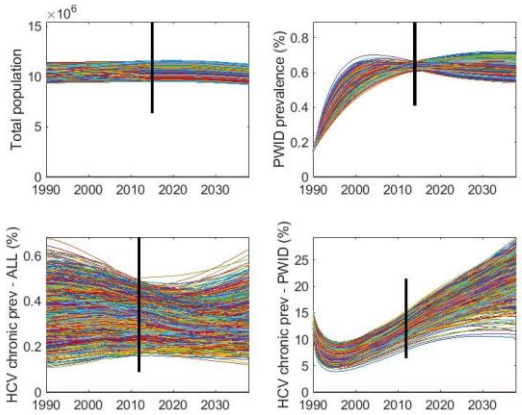

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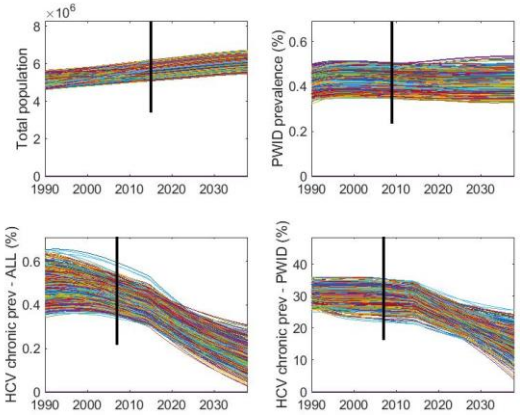

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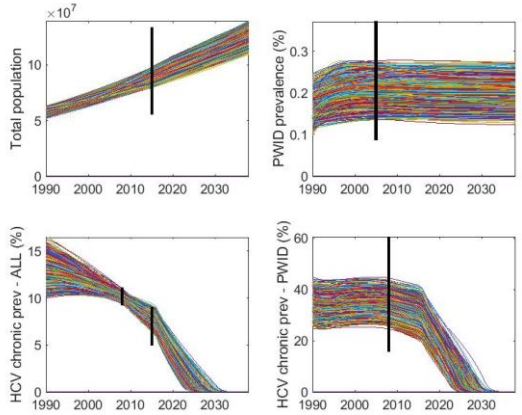

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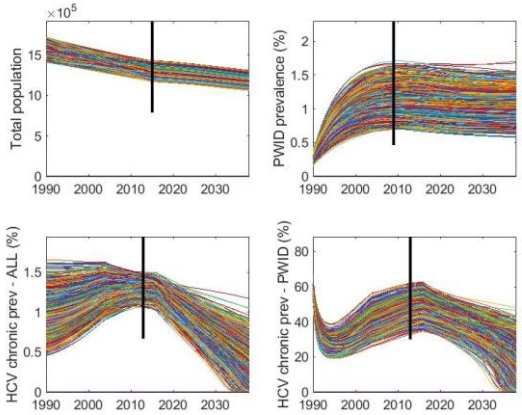

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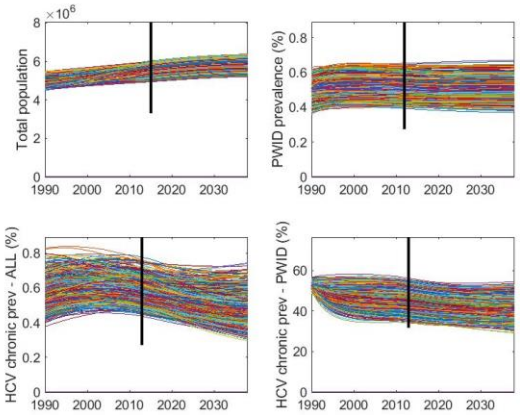

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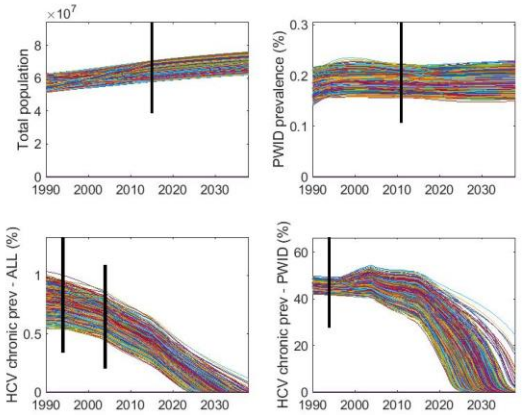

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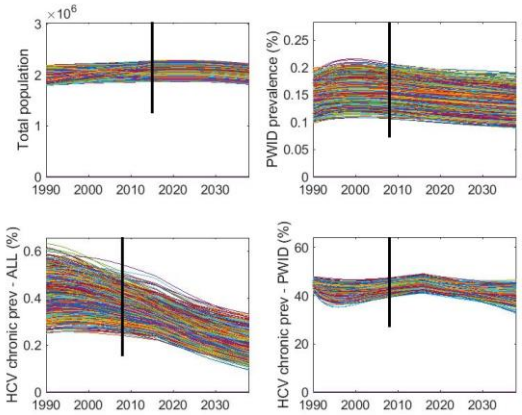

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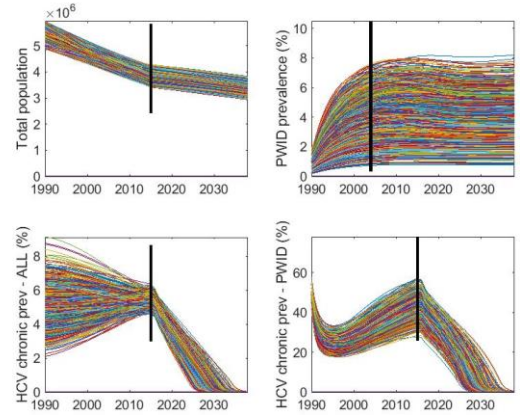

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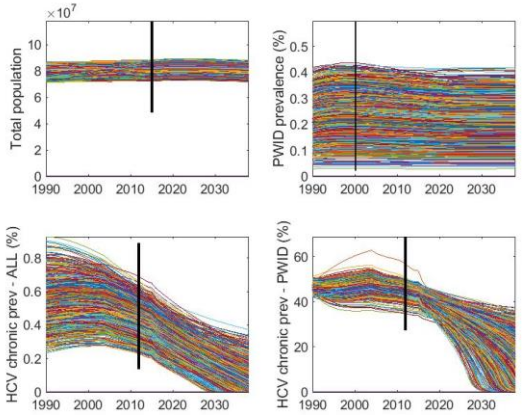

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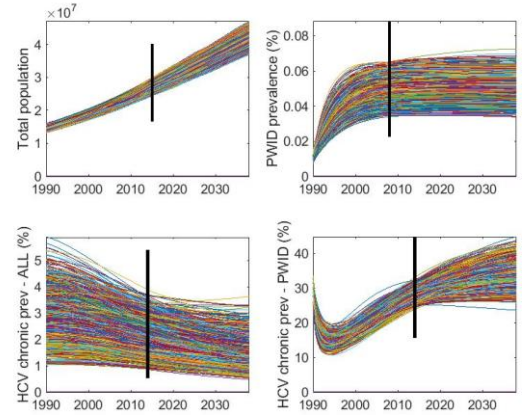

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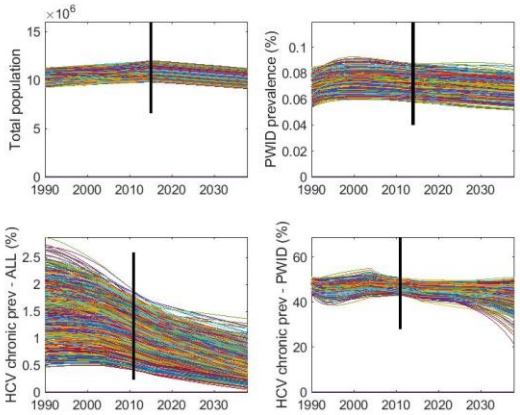

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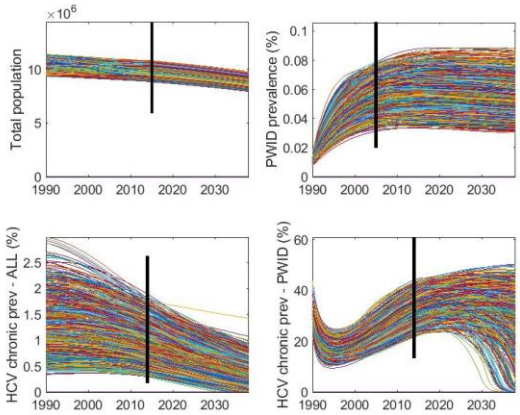

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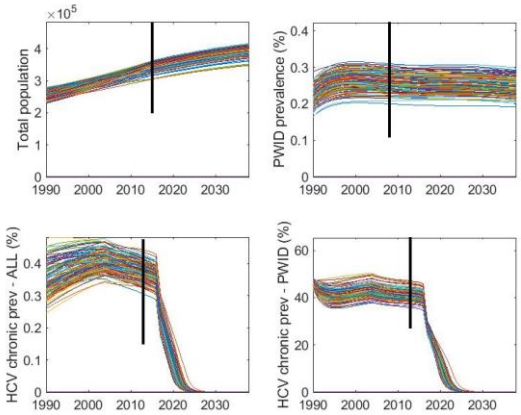

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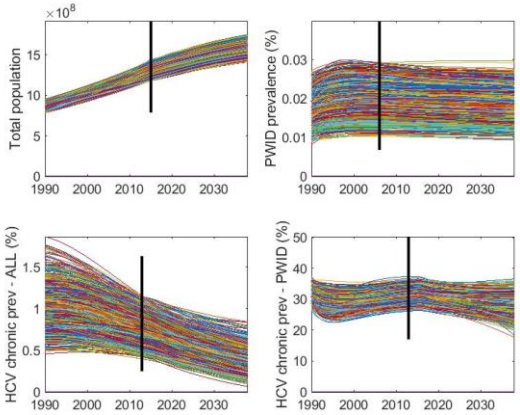

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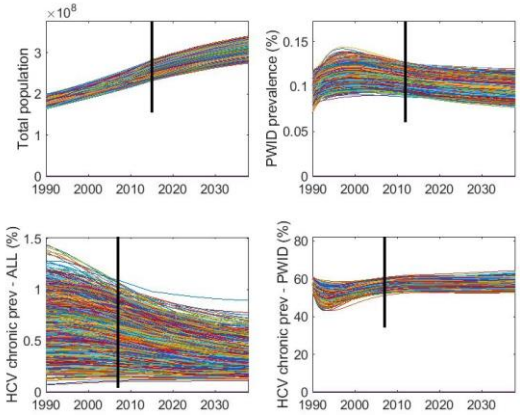

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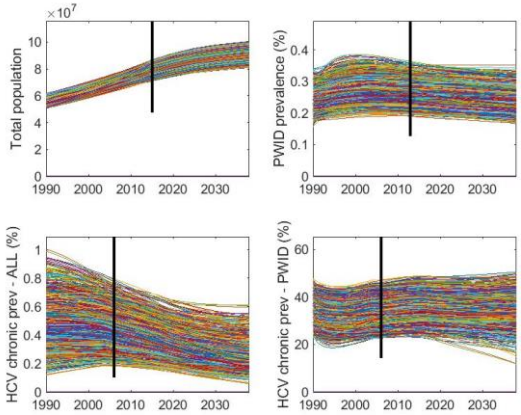

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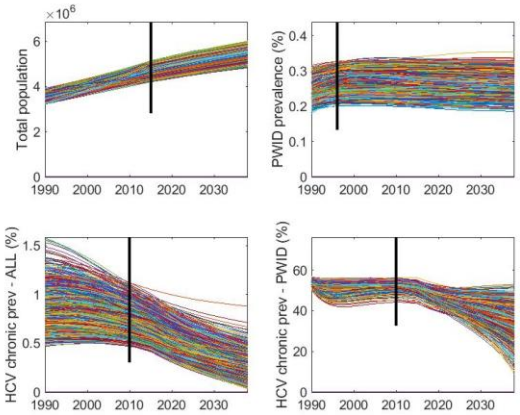

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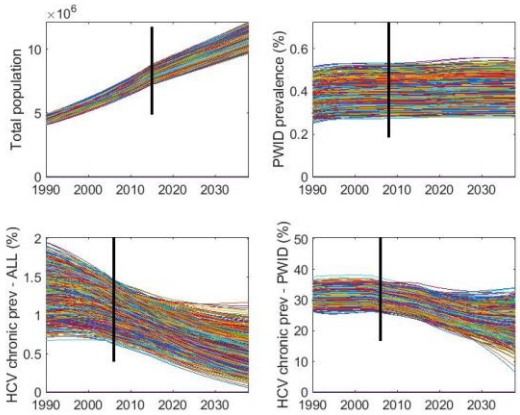

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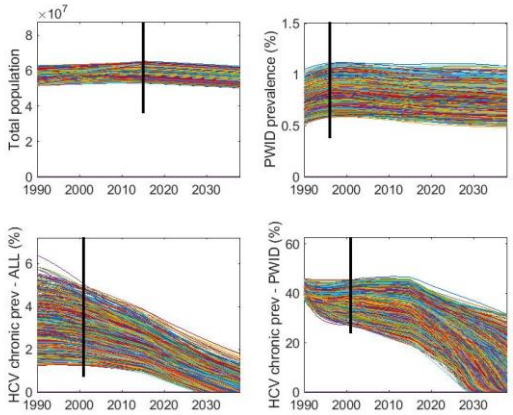
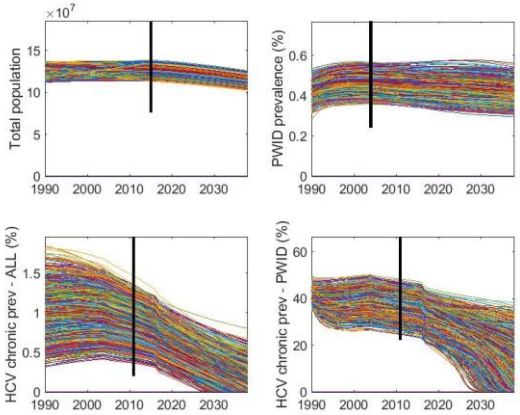


Japan



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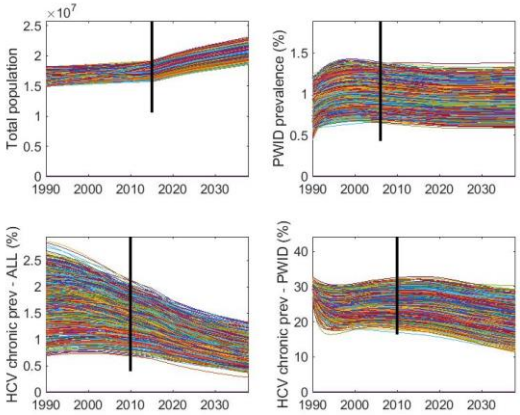

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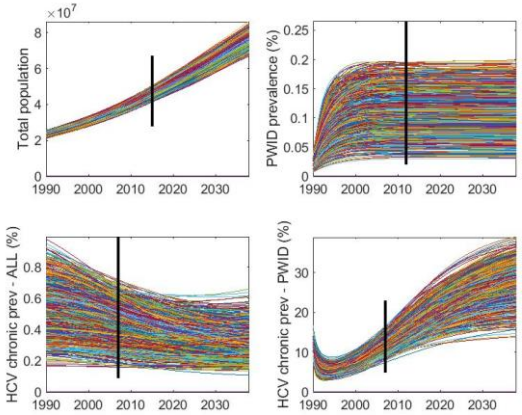

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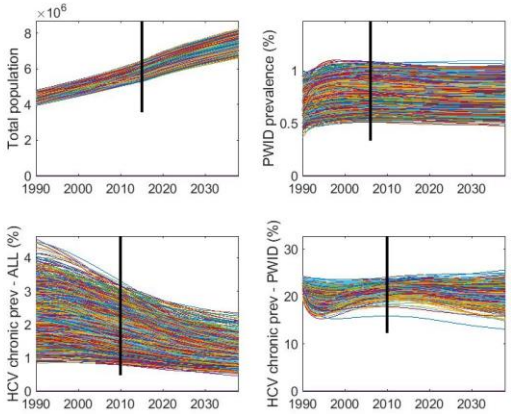

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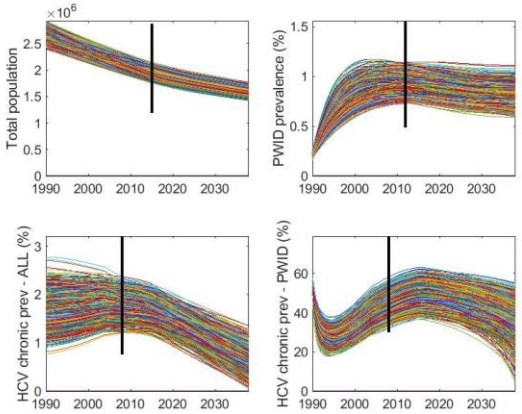

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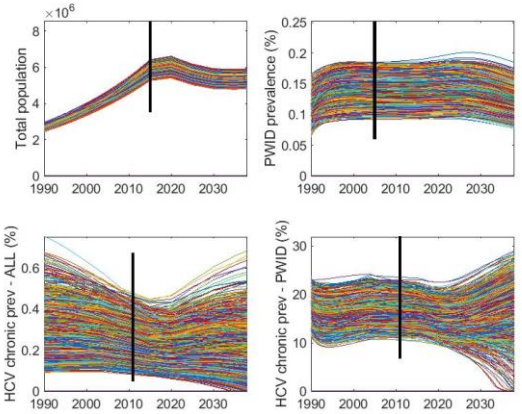

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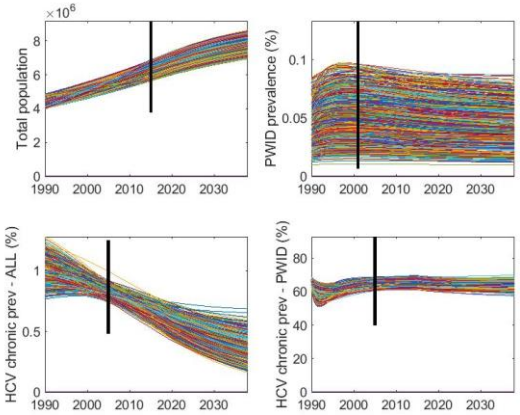

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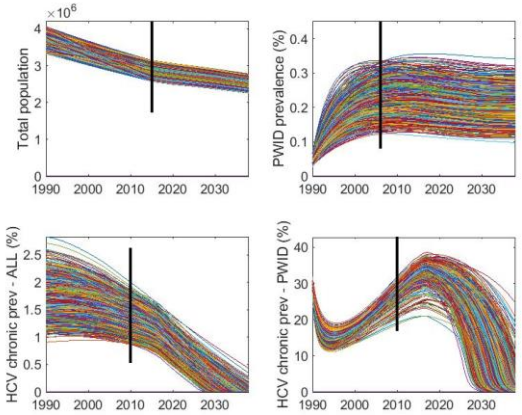
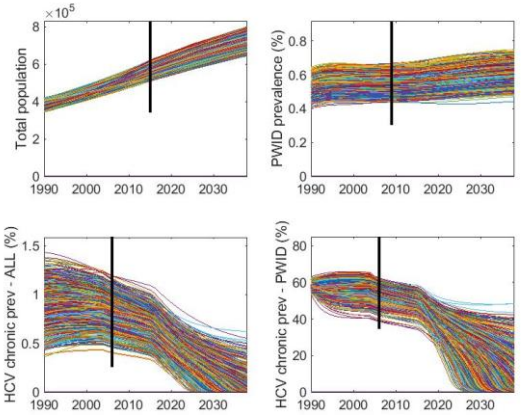
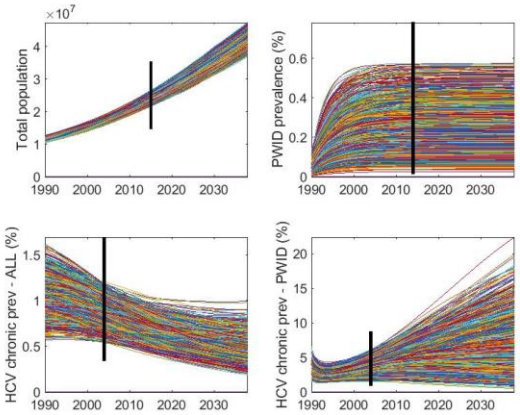


Luxembourg



Madagascar



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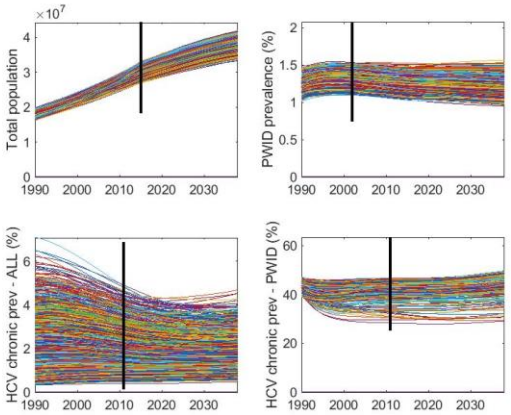

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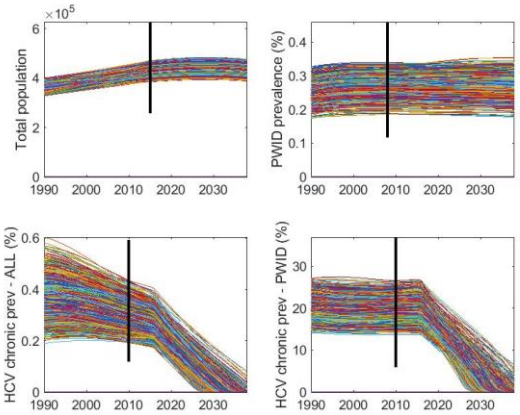

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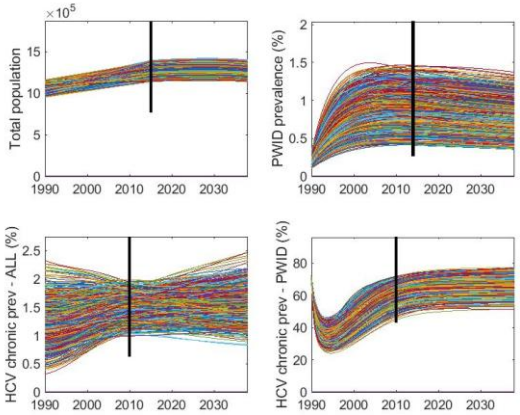
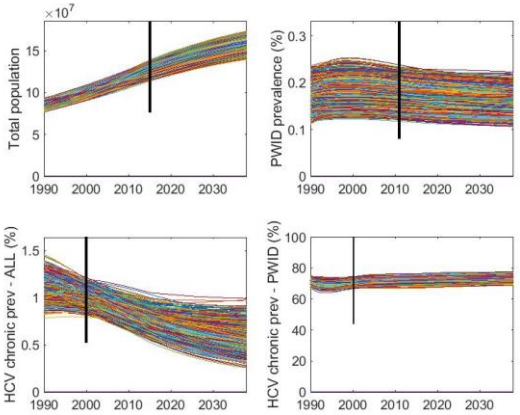
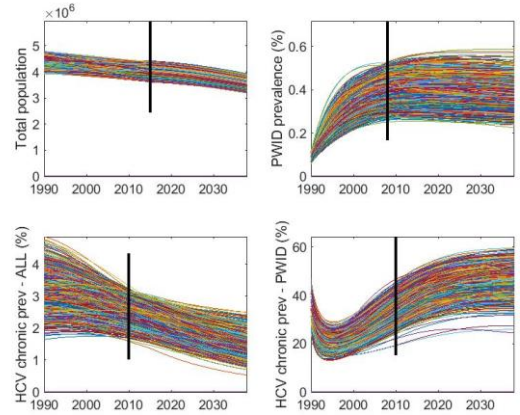


Mexico



Moldova



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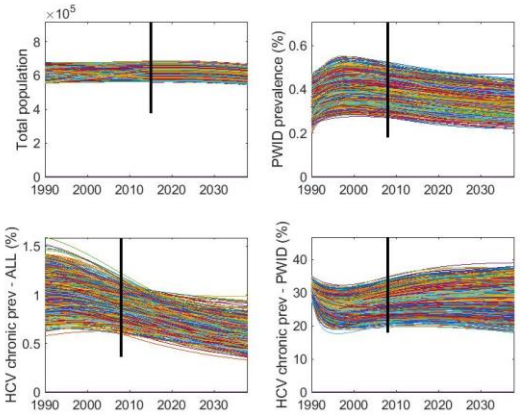

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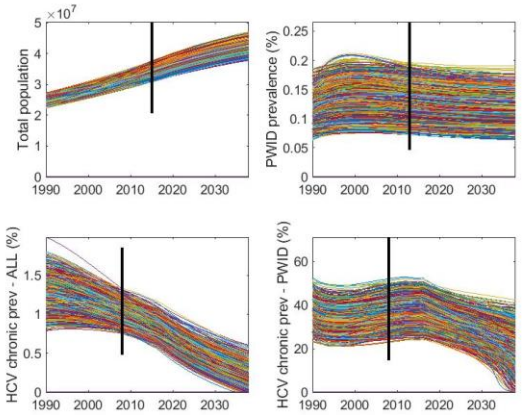

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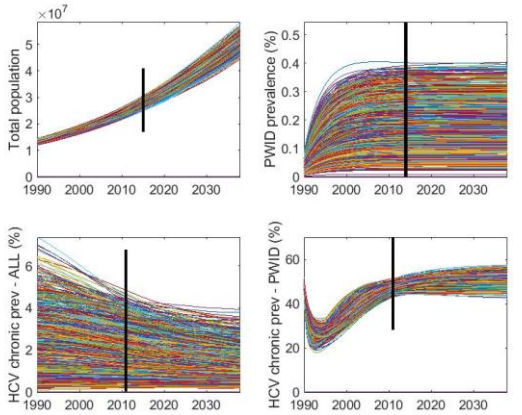

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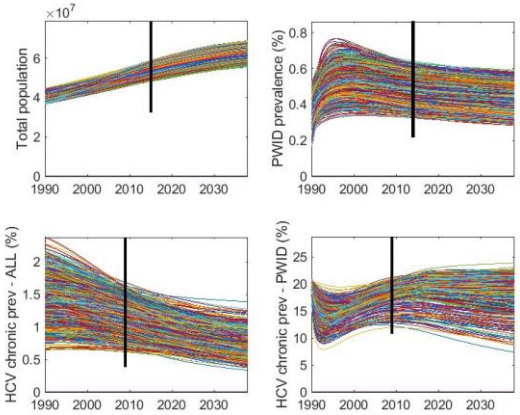

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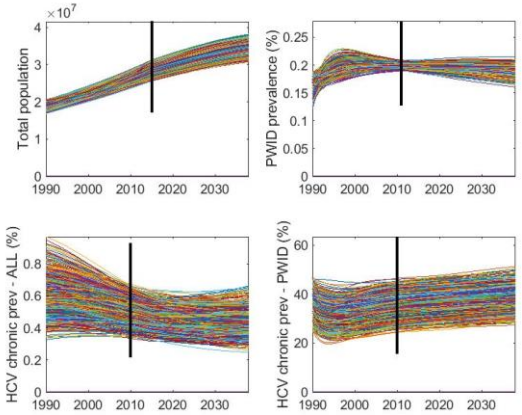

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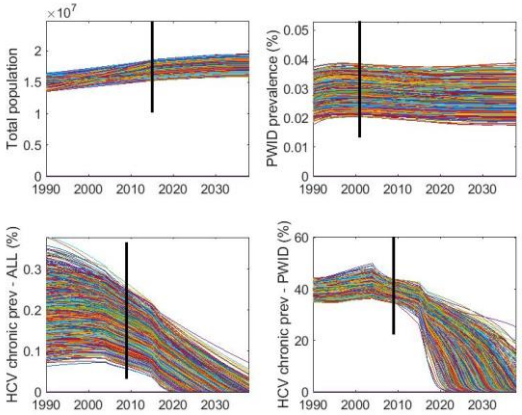

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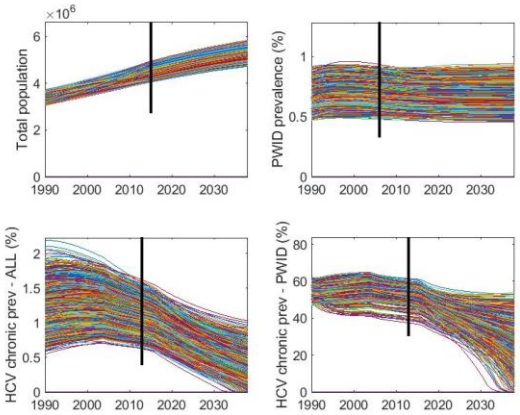

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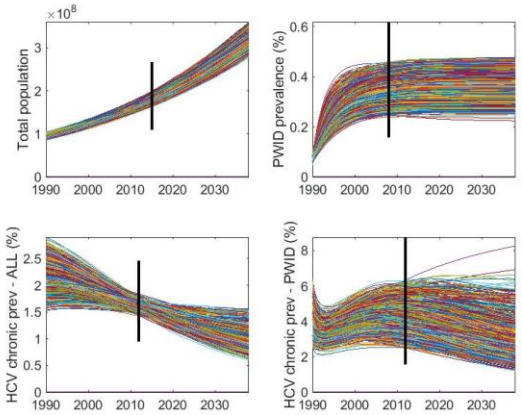

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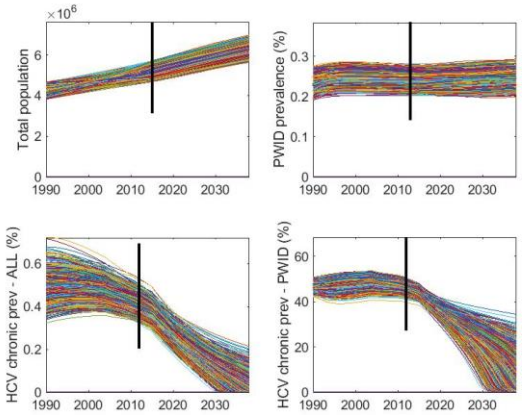

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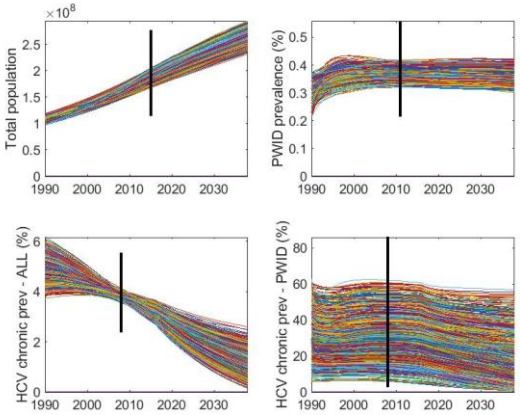

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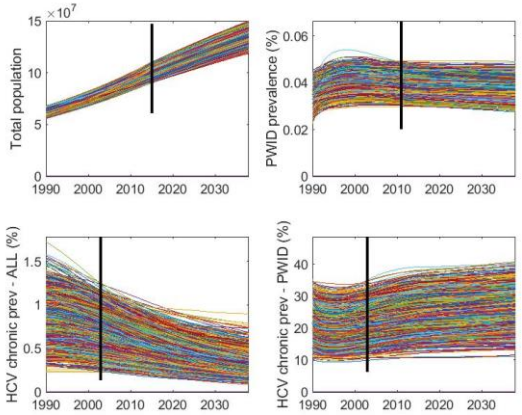

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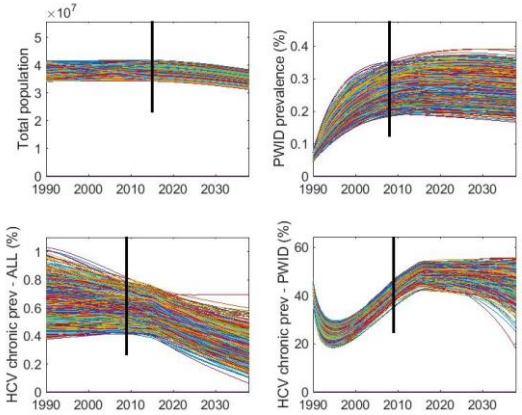

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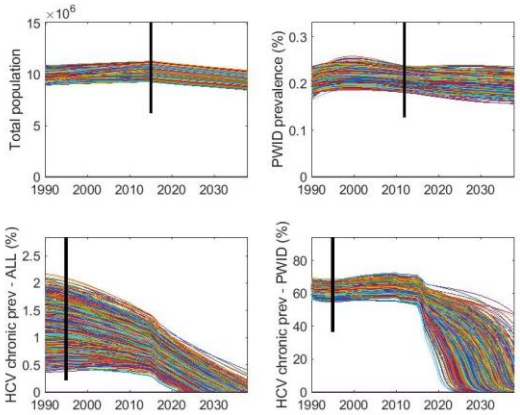

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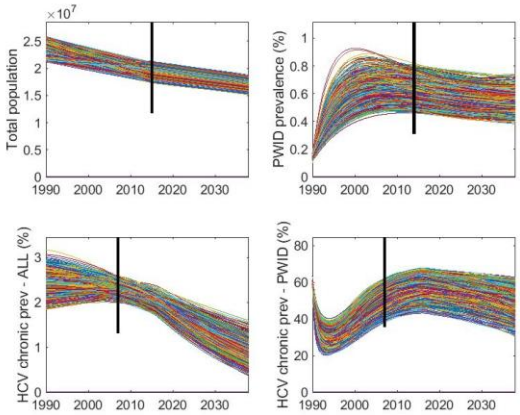

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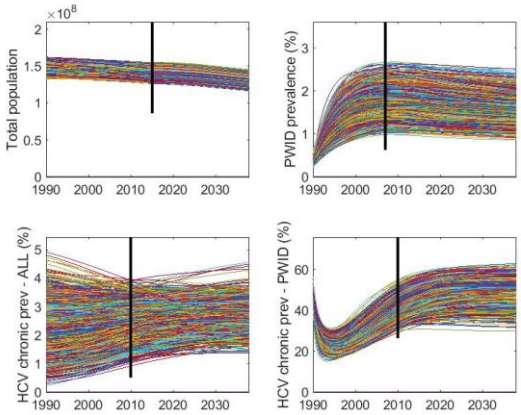

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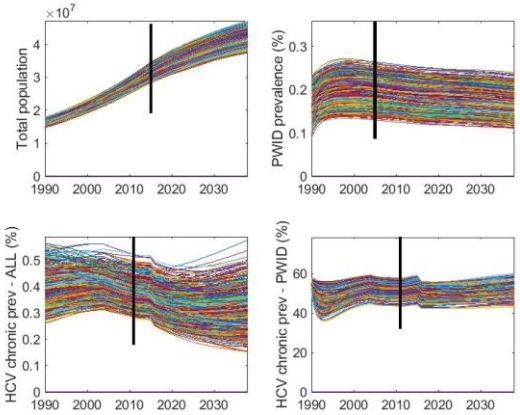

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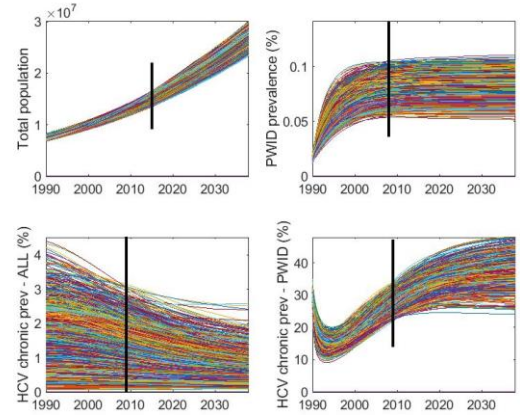

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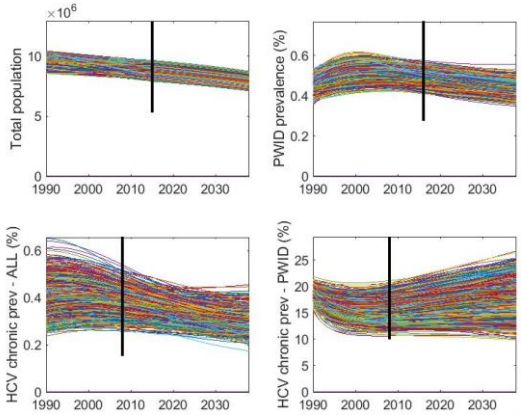

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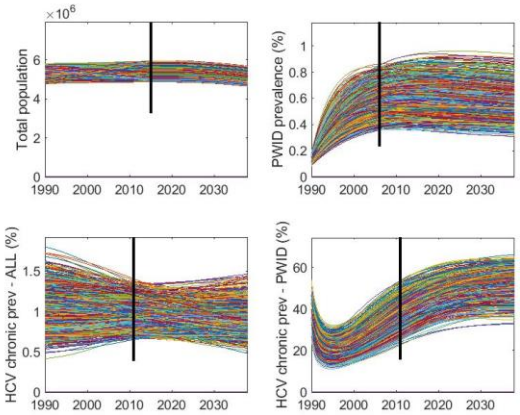

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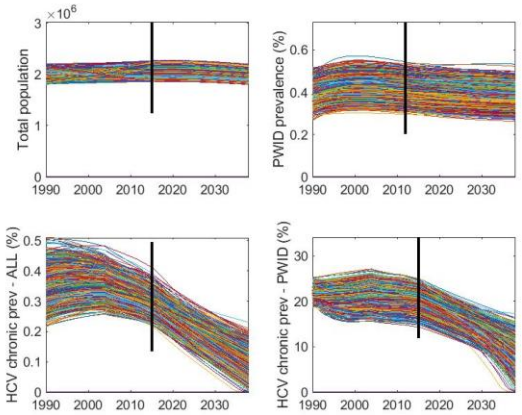

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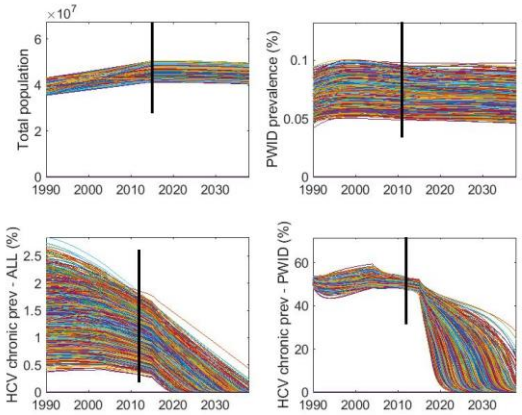

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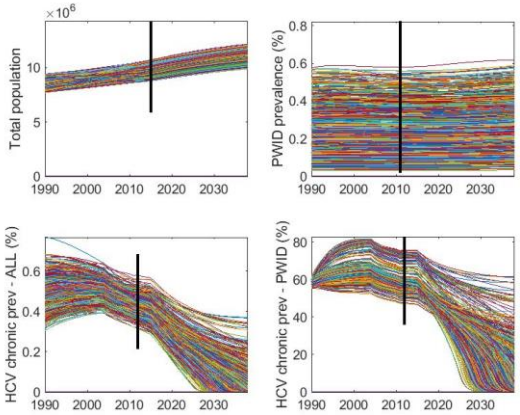

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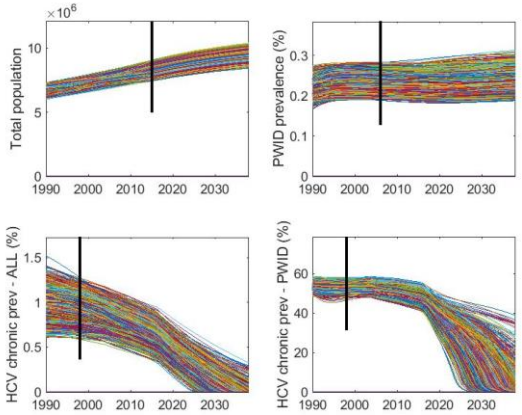

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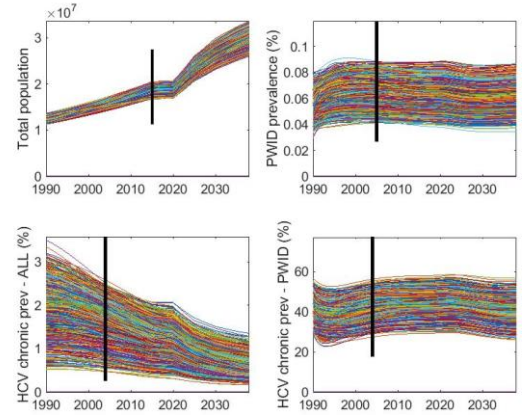

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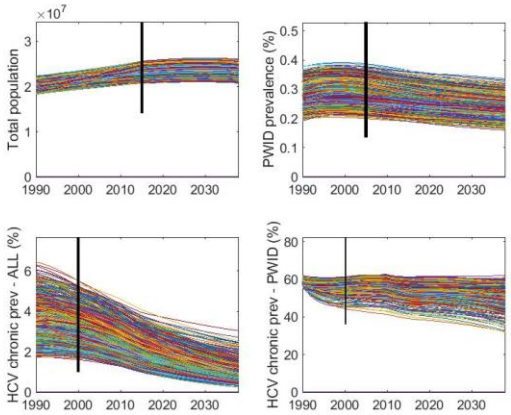

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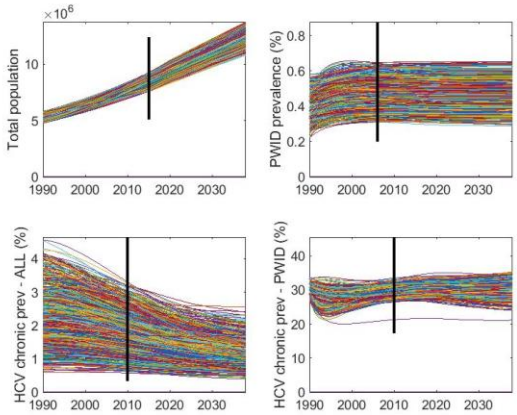

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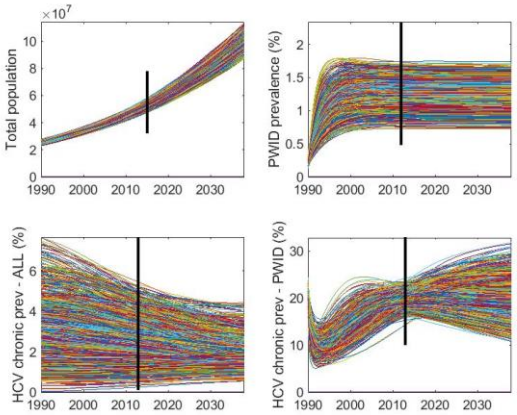

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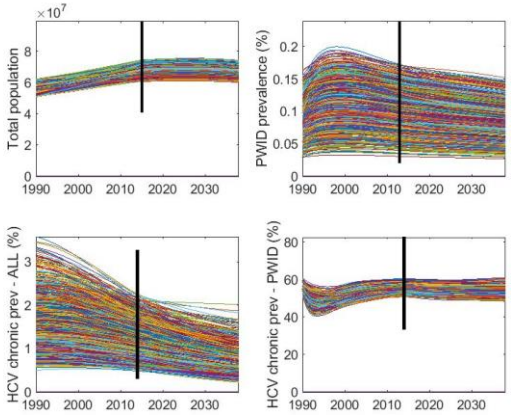

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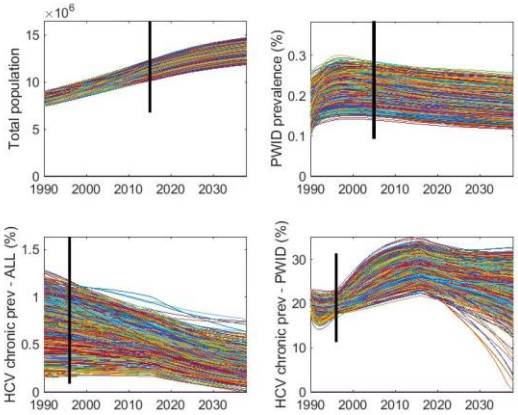

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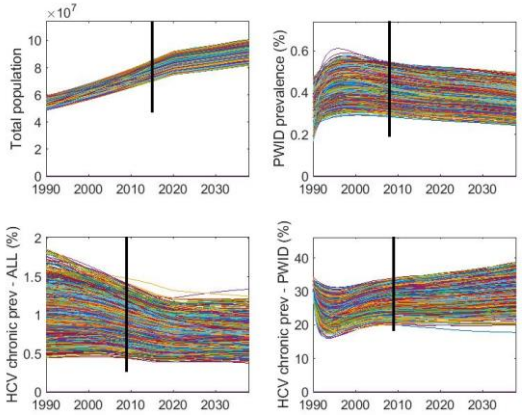

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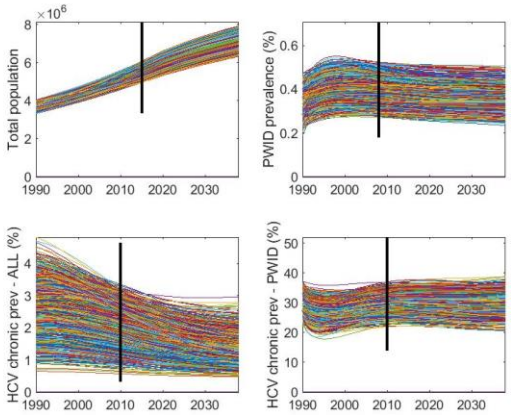

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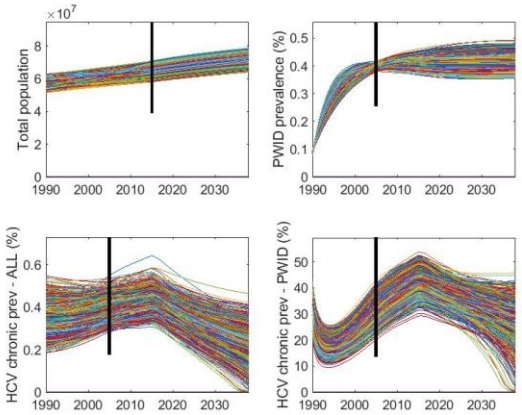

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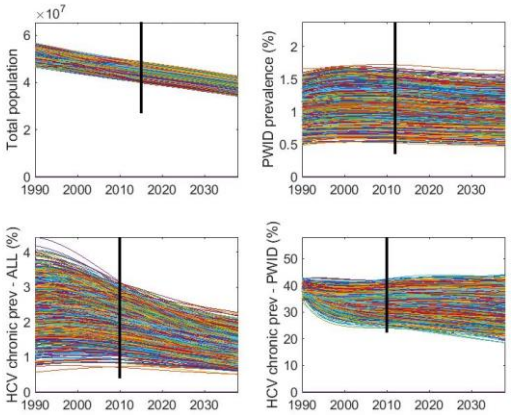

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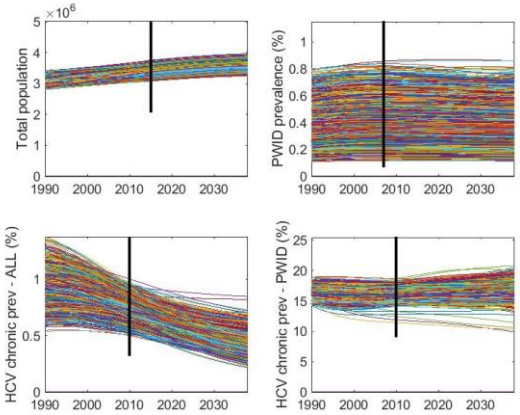
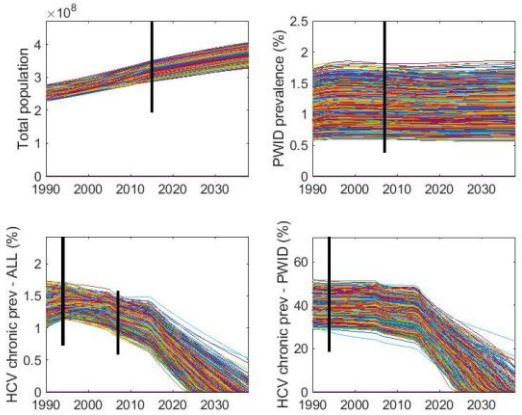
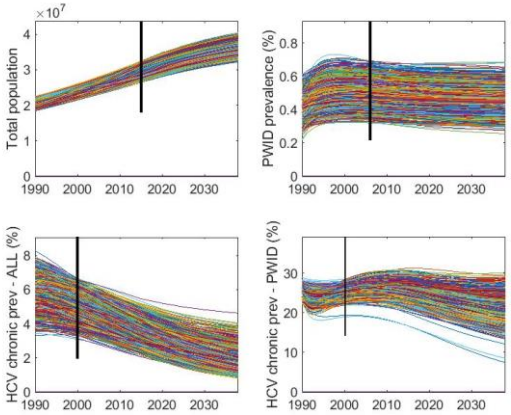


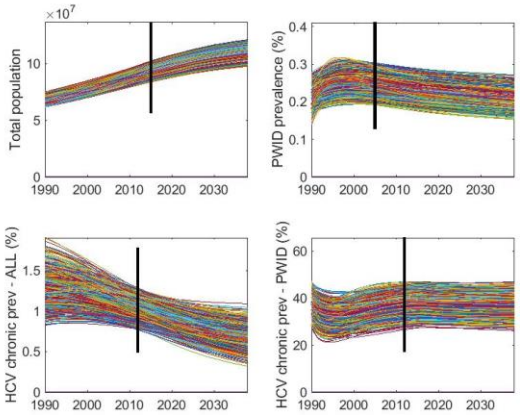
USA



Uzbekistan



Viet Nam



The HCV prevalence for many runs appears to curve upwards for runs that previously had decreasing prevalence as the transmission rates were fit for the population change for 1990 and 2015. The same transmission rates are then used from 2015 onwards, however, the UN projected population estimates often increase at a slower rate after 2015, meaning the same transmission rate causes an increase in prevalence. This also applies to other countries.

The HCV prevalence among the general population and PWID reaches 0% for some runs in countries where treatment numbers are already high, such as Egypt, France, and the USA. This is because the model assumes these annual treatment numbers continue for future years. The model does not include diagnosis as a barrier to starting treatment as screening patterns are difficult to predict and are likely to evolve to maintain treatment rates. For example, Egypt screened 30 million people (roughly a quarter of their population) in a period of around four months starting in October 2018(11).

Appendix table 7.4: Sensitivity analyses for the population attributable fraction (tPAF) of injecting drug use (IDU) to hepatitis C virus (HCV) transmission from 2018 to 2030, with 95% credibility intervals.

	Population Attributable Fraction of injecting drug use to hepatitis C virus transmission 2018-2030					
Country	**Main analysis**	**Stable general population HCV prevalence**	**Decreasing PWID HCV prevalence***	**Stable proportion of adults that are PWID in 1990 in EE and SSA****	**Altered treatment rates for PWID and people with cirrhosis*****	**Varied HCV epidemic trajectories by region**
Global	**43% (24%, 66%)**	**33% (20%, 54%)**	**43% (23%, 66%)**	**43% (25%, 66%)**	**43% (23%, 66%)**	**30% (15%, 51%)**
Central Asia	**36% (18%, 76%)**	**23% (13%, 44%)**	**36% (19%, 77%)**	**36% (18%, 76%)**	**36% (18%, 76%)**	**4% (1%, 15%)**
Kazakhstan	99% (71%, 100%)	79% (57%, 100%)	99% (70%, 100%)	99% (71%, 100%)	99% (71%, 100%)	45% (9%, 100%)
Kyrgyzstan	52% (22%, 95%)	36% (17%, 85%)	51% (22%, 97%)	52% (22%, 95%)	52% (22%, 95%)	8% (1%, 47%)
Tajikistan	41% (17%, 84%)	28% (14%, 55%)	40% (17%, 86%)	41% (17%, 84%)	41% (17%, 84%)	6% (1%, 36%)
Turkmenistan	33% (16%, 77%)	21% (12%, 59%)	33% (16%, 80%)	33% (16%, 77%)	33% (16%, 77%)	4% (0%, 30%)
Uzbekistan	21% (9%, 68%)	13% (6%, 25%)	20% (9%, 68%)	21% (9%, 68%)	21% (9%, 68%)	1% (0%, 7%)
Eastern Europe	**96% (65%, 99%)**	**81% (54%, 96%)**	**96% (66%, 99%)**	**96% (70%, 99%)**	**96% (65%, 99%)**	**45% (10%, 86%)**
Armenia	79% (41%, 100%)	45% (27%, 68%)	79% (41%, 100%)	74% (31%, 100%)	79% (41%, 100%)	4% (0%, 28%)
Azerbaijan	52% (31%, 76%)	36% (25%, 56%)	52% (31%, 77%)	51% (27%, 92%)	52% (31%, 76%)	5% (0%, 21%)
Belarus	100% (67%, 100%)	72% (40%, 100%)	100% (67%, 100%)	100% (63%, 100%)	100% (67%, 100%)	32% (6%, 90%)
Bosnia	100% (97%, 100%)	100% (89%, 100%)	100% (97%, 100%)	100% (100%, 100%)	100% (97%, 100%)	96% (59%, 100%)
Bulgaria	100% (63%, 100%)	72% (52%, 100%)	100% (63%, 100%)	100% (65%, 100%)	100% (63%, 100%)	36% (8%, 84%)
Czech Republic	89% (69%, 100%)	76% (57%, 96%)	89% (68%, 100%)	94% (56%, 100%)	88% (69%, 100%)	50% (17%, 90%)
Estonia	100% (96%, 100%)	100% (89%, 100%)	100% (95%, 100%)	100% (96%, 100%)	100% (93%, 100%)	93% (54%, 100%)
Georgia	100% (68%, 100%)	91% (60%, 100%)	100% (68%, 100%)	100% (57%, 100%)	100% (73%, 100%)	61% (11%, 100%)
Hungary	30% (13%, 74%)	16% (6%, 37%)	29% (12%, 73%)	20% (6%, 71%)	30% (13%, 74%)	5% (1%, 23%)
Latvia	100% (85%, 100%)	92% (73%, 100%)	100% (85%, 100%)	100% (91%, 100%)	100% (83%, 100%)	51% (15%, 100%)
Lithuania	76% (37%, 100%)	42% (27%, 65%)	76% (37%, 100%)	72% (32%, 100%)	78% (38%, 100%)	9% (0%, 32%)
Moldova	56% (27%, 100%)	30% (20%, 48%)	56% (27%, 100%)	48% (19%, 100%)	56% (27%, 100%)	6% (0%, 25%)
Poland	87% (62%, 100%)	65% (53%, 89%)	87% (62%, 100%)	96% (56%, 100%)	86% (62%, 100%)	28% (12%, 64%)
Romania	100% (64%, 100%)	70% (57%, 100%)	100% (64%, 100%)	100% (78%, 100%)	100% (62%, 100%)	33% (12%, 76%)
Russia	100% (73%, 100%)	90% (61%, 100%)	100% (74%, 100%)	100% (80%, 100%)	100% (73%, 100%)	60% (13%, 100%)
Slovakia	86% (61%, 100%)	70% (50%, 100%)	87% (61%, 100%)	96% (50%, 100%)	86% (60%, 100%)	38% (8%, 76%)
Ukraine	100% (53%, 100%)	76% (42%, 100%)	100% (51%, 100%)	100% (53%, 100%)	100% (53%, 100%)	30% (6%, 99%)
Australasia	**69% (43%, 100%)**	**52% (34%, 85%)**	**69% (43%, 100%)**	**69% (43%, 100%)**	**74% (49%, 100%)**	**48% (29%, 80%)**
Australia	66% (41%, 100%)	48% (32%, 81%)	65% (40%, 100%)	66% (41%, 100%)	72% (48%, 100%)	44% (27%, 75%)
New Zealand	82% (55%, 100%)	70% (47%, 100%)	84% (56%, 100%)	82% (55%, 100%)	80% (54%, 100%)	68% (37%, 99%)

	Population Attributable Fraction of injecting drug use to Hepatitis C virus transmission 2018-2030					
Country	**Main analysis**	**Stable general population HCV prevalence**	**Decreasing PWID HCV prevalence***	**Stable proportion of adults that are PWID in 1990 in EE and SSA****	**Altered treatment rates for PWID and people with cirrhosis*****	**Varied HCV epidemic trajectories by region**
East & Southeast Asia	**58% (29%, 95%)**	**42% (25%, 73%)**	**59% (29%, 97%)**	**58% (29%, 95%)**	**59% (29%, 95%)**	**44% (24%, 75%)**
China	56% (28%, 95%)	39% (24%, 68%)	57% (27%, 99%)	56% (28%, 95%)	56% (28%, 95%)	45% (24%, 72%)
Indonesia	73% (35%, 100%)	48% (23%, 100%)	74% (35%, 100%)	73% (35%, 100%)	73% (35%, 100%)	39% (19%, 95%)
Japan	100% (71%, 100%)	96% (59%, 100%)	100% (72%, 100%)	100% (71%, 100%)	100% (70%, 100%)	100% (78%, 100%)
Malaysia	67% (26%, 100%)	52% (24%, 100%)	68% (26%, 100%)	67% (26%, 100%)	67% (26%, 100%)	52% (23%, 100%)
Myanmar	72% (34%, 100%)	59% (33%, 98%)	74% (33%, 100%)	72% (34%, 100%)	72% (34%, 100%)	51% (27%, 88%)
Philippines	14% (4%, 40%)	8% (3%, 19%)	12% (4%, 38%)	14% (4%, 40%)	14% (4%, 40%)	7% (3%, 21%)
Taiwan	62% (19%, 100%)	27% (12%, 56%)	62% (19%, 100%)	62% (19%, 100%)	61% (19%, 100%)	36% (15%, 68%)
Thailand	41% (15%, 100%)	24% (10%, 64%)	41% (15%, 100%)	41% (15%, 100%)	41% (15%, 100%)	24% (9%, 65%)
Viet Nam	56% (30%, 98%)	41% (25%, 69%)	57% (30%, 100%)	56% (30%, 98%)	57% (30%, 98%)	36% (23%, 69%)
South Asia	**13% (4%, 30%)**	**9% (4%, 22%)**	**13% (3%, 30%)**	**13% (4%, 30%)**	**13% (4%, 30%)**	**10% (3%, 20%)**
Afghanistan	61% (35%, 99%)	51% (29%, 98%)	62% (34%, 100%)	61% (35%, 99%)	61% (35%, 99%)	52% (25%, 97%)
Bangladesh	15% (5%, 46%)	9% (4%, 31%)	14% (5%, 45%)	15% (5%, 46%)	15% (5%, 46%)	7% (4%, 28%)
India	5% (3%, 13%)	3% (2%, 9%)	5% (2%, 13%)	5% (3%, 13%)	5% (3%, 13%)	4% (2%, 8%)
Iran	84% (55%, 100%)	67% (42%, 100%)	86% (55%, 100%)	84% (55%, 100%)	84% (54%, 100%)	82% (52%, 100%)
Nepal	70% (47%, 100%)	51% (32%, 97%)	72% (47%, 100%)	70% (47%, 100%)	70% (47%, 100%)	48% (31%, 83%)
Pakistan	19% (1%, 48%)	13% (3%, 33%)	18% (1%, 49%)	19% (1%, 48%)	19% (1%, 48%)	12% (1%, 26%)
North America	**77% (54%, 100%)**	**67% (46%, 93%)**	**74% (50%, 100%)**	**80% (56%, 100%)**	**70% (33%, 100%)**	**74% (55%, 100%)**
Canada	82% (55%, 100%)	72% (46%, 100%)	83% (56%, 100%)	82% (55%, 100%)	81% (53%, 100%)	80% (54%, 100%)
USA	77% (54%, 100%)	67% (46%, 93%)	73% (49%, 100%)	80% (56%, 100%)	69% (31%, 100%)	74% (55%, 100%)
Western Europe	**83% (54%, 95%)**	**65% (41%, 89%)**	**83% (54%, 95%)**	**83% (52%, 95%)**	**84% (54%, 95%)**	**62% (39%, 86%)**
Albania	65% (25%, 100%)	28% (17%, 48%)	63% (24%, 100%)	64% (26%, 100%)	65% (25%, 100%)	6% (2%, 21%)
Austria	100% (82%, 100%)	94% (68%, 100%)	100% (82%, 100%)	100% (82%, 100%)	100% (81%, 100%)	100% (73%, 100%)
Belgium	96% (56%, 100%)	82% (48%, 100%)	97% (55%, 100%)	96% (56%, 100%)	96% (57%, 100%)	74% (46%, 100%)
Croatia	72% (37%, 100%)	42% (26%, 71%)	72% (35%, 100%)	72% (37%, 100%)	71% (37%, 100%)	14% (4%, 44%)
Cyprus	37% (13%, 78%)	18% (8%, 53%)	35% (12%, 79%)	37% (13%, 78%)	37% (13%, 78%)	19% (8%, 45%)
Denmark	92% (59%, 100%)	70% (48%, 100%)	95% (58%, 100%)	92% (59%, 100%)	92% (60%, 100%)	71% (47%, 100%)
FYROM	91% (56%, 100%)	72% (46%, 100%)	93% (56%, 100%)	91% (56%, 100%)	91% (56%, 100%)	32% (9%, 80%)
Finland	100% (88%, 100%)	100% (76%, 100%)	100% (88%, 100%)	100% (88%, 100%)	100% (87%, 100%)	100% (79%, 100%)
France	93% (59%, 100%)	69% (53%, 98%)	92% (56%, 100%)	96% (61%, 100%)	95% (65%, 100%)	67% (45%, 91%)
Germany	86% (47%, 100%)	76% (31%, 100%)	88% (41%, 100%)	86% (47%, 100%)	85% (43%, 100%)	69% (28%, 100%)

	Population Attributable Fraction of injecting drug use to Hepatitis C virus transmission 2018-2030					
Country	**Main analysis**	**Stable general population HCV prevalence**	**Decreasing PWID HCV prevalence***	**Stable proportion of adults that are PWID in 1990 in EE and SSA****	**Altered treatment rates for PWID and people with cirrhosis*****	**Varied HCV epidemic trajectories by region**
Greece	23% (10%, 65%)	12% (7%, 25%)	23% (10%, 67%)	23% (10%, 65%)	22% (10%, 63%)	13% (7%, 31%)
Iceland	100% (96%, 100%)	100% (88%, 100%)	100% (98%, 100%)	100% (96%, 100%)	100% (84%, 100%)	100% (89%, 100%)
Ireland	82% (50%, 100%)	56% (35%, 97%)	83% (50%, 100%)	82% (50%, 100%)	81% (49%, 100%)	62% (42%, 100%)
Italy	100% (55%, 100%)	77% (38%, 100%)	100% (54%, 100%)	100% (55%, 100%)	100% (56%, 100%)	76% (39%, 100%)
Luxembourg	96% (76%, 100%)	92% (67%, 100%)	97% (76%, 100%)	96% (76%, 100%)	95% (75%, 100%)	87% (63%, 100%)
Malta	83% (43%, 100%)	61% (36%, 96%)	84% (43%, 100%)	83% (43%, 100%)	84% (46%, 100%)	61% (34%, 100%)
Montenegro	100% (68%, 100%)	81% (51%, 100%)	100% (68%, 100%)	100% (68%, 100%)	100% (68%, 100%)	39% (13%, 100%)
Netherlands	57% (20%, 88%)	33% (18%, 70%)	56% (19%, 90%)	57% (20%, 88%)	61% (20%, 90%)	35% (20%, 69%)
Norway	85% (61%, 100%)	69% (53%, 100%)	86% (61%, 100%)	85% (61%, 100%)	84% (60%, 100%)	73% (54%, 100%)
Portugal	100% (72%, 100%)	76% (43%, 100%)	100% (71%, 100%)	100% (72%, 100%)	100% (71%, 100%)	71% (40%, 100%)
Serbia	100% (88%, 100%)	98% (73%, 100%)	100% (89%, 100%)	100% (88%, 100%)	100% (88%, 100%)	64% (27%, 100%)
Slovenia	97% (68%, 100%)	84% (54%, 100%)	100% (68%, 100%)	97% (68%, 100%)	95% (67%, 100%)	84% (56%, 100%)
Spain	31% (15%, 70%)	19% (8%, 53%)	31% (14%, 71%)	31% (15%, 70%)	34% (15%, 74%)	19% (9%, 42%)
Sweden	90% (41%, 100%)	75% (32%, 100%)	92% (40%, 100%)	90% (41%, 100%)	88% (40%, 100%)	78% (30%, 100%)
Switzerland	92% (52%, 100%)	57% (35%, 91%)	92% (49%, 100%)	92% (52%, 100%)	92% (54%, 100%)	59% (34%, 92%)
UK	97% (86%, 100%)	89% (76%, 100%)	98% (86%, 100%)	100% (80%, 100%)	97% (86%, 100%)	87% (75%, 100%)
Sub-Saharan Africa	**13% (3%, 42%)**	**11% (2%, 36%)**	**13% (2%, 42%)**	**12% (2%, 43%)**	**13% (3%, 42%)**	**12% (2%, 41%)**
Ghana	3% (1%, 7%)	2% (1%, 5%)	3% (1%, 7%)	2% (1%, 7%)	3% (1%, 7%)	2% (1%, 6%)
Kenya	29% (15%, 56%)	23% (11%, 47%)	28% (14%, 54%)	22% (8%, 52%)	29% (15%, 56%)	26% (11%, 51%)
Madagascar	6% (1%, 29%)	5% (0%, 15%)	6% (0%, 26%)	3% (0%, 11%)	6% (1%, 29%)	5% (1%, 22%)
Mauritius	88% (55%, 100%)	73% (48%, 100%)	89% (55%, 100%)	100% (63%, 100%)	88% (55%, 100%)	82% (51%, 100%)
Mozambique	20% (5%, 64%)	14% (3%, 54%)	20% (5%, 64%)	19% (4%, 56%)	20% (5%, 64%)	22% (3%, 69%)
Nigeria	1% (0%, 3%)	1% (0%, 3%)	1% (0%, 3%)	1% (0%, 4%)	1% (0%, 3%)	1% (0%, 4%)
Senegal	11% (3%, 40%)	6% (3%, 17%)	11% (3%, 39%)	8% (2%, 43%)	11% (3%, 40%)	9% (3%, 27%)
Tanzania	34% (13%, 95%)	33% (10%, 86%)	34% (13%, 96%)	38% (12%, 100%)	34% (13%, 95%)	32% (11%, 83%)
Latin America	**75% (48%, 98%)**	**54% (39%, 80%)**	**76% (48%, 99%)**	**75% (48%, 99%)**	**75% (48%, 98%)**	**64% (45%, 88%)**
Argentina	60% (32%, 98%)	37% (23%, 64%)	60% (32%, 100%)	61% (31%, 100%)	60% (32%, 98%)	50% (29%, 90%)
Brazil	87% (59%, 100%)	70% (51%, 100%)	89% (59%, 100%)	87% (59%, 100%)	87% (59%, 100%)	78% (56%, 100%)
Mexico	55% (30%, 95%)	32% (24%, 52%)	56% (30%, 96%)	55% (30%, 95%)	55% (30%, 95%)	43% (29%, 63%)
Uruguay	48% (22%, 99%)	29% (11%, 68%)	46% (20%, 100%)	48% (22%, 99%)	48% (22%, 99%)	41% (19%, 75%)

	Population Attributable Fraction of injecting drug use to Hepatitis C virus transmission 2018-2030					
Country	**Main analysis**	**Stable general population HCV prevalence**	**Decreasing PWID HCV prevalence***	**Stable proportion of adults that are PWID in 1990 in EE and SSA****	**Altered treatment rates for PWID and people with cirrhosis*****	**Varied HCV epidemic trajectories by region**
Middle East & North Africa	**16% (8%, 26%)**	**11% (5%, 22%)**	**15% (8%, 26%)**	**16% (8%, 28%)**	**17% (8%, 29%)**	**14% (7%, 24%)**
Egypt	5% (2%, 10%)	3% (1%, 8%)	4% (2%, 10%)	5% (2%, 12%)	6% (2%, 13%)	4% (2%, 9%)
Israel	38% (19%, 67%)	25% (16%, 52%)	34% (18%, 65%)	38% (19%, 67%)	38% (19%, 67%)	28% (16%, 51%)
Lebanon	49% (18%, 89%)	33% (14%, 82%)	48% (17%, 91%)	49% (18%, 89%)	50% (19%, 89%)	45% (18%, 99%)
Libya	38% (12%, 92%)	22% (9%, 51%)	39% (12%, 93%)	38% (12%, 92%)	38% (12%, 92%)	36% (15%, 68%)
Morocco	41% (17%, 75%)	21% (13%, 40%)	41% (16%, 76%)	41% (17%, 75%)	41% (17%, 75%)	35% (17%, 62%)
Saudi Arabia	87% (64%, 100%)	84% (58%, 100%)	88% (65%, 100%)	87% (64%, 100%)	85% (62%, 100%)	96% (65%, 100%)
Syria	17% (6%, 47%)	8% (4%, 27%)	17% (6%, 47%)	17% (6%, 47%)	17% (6%, 47%)	14% (6%, 35%)
Tunisia	78% (42%, 100%)	55% (28%, 86%)	77% (41%, 100%)	78% (42%, 100%)	78% (43%, 100%)	80% (43%, 100%)
Turkey	92% (58%, 100%)	74% (39%, 100%)	95% (59%, 100%)	92% (58%, 100%)	92% (59%, 100%)	90% (49%, 100%)

* Decreasing at the same rate as the HCV prevalence among the general population

** EE: Eastern Europe; SSA: Sub-Saharan Africa

*** Treatment numbers remain the same as in the main analysis but treatment rates among PWID are halved and among people with cirrhosis are doubled. This can also mean an alteration in the treatment rates (either an increase or a decrease depending on the country) for people that do not inject drugs and do not have cirrhosis.